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ACTION OF SULPHUR COMPOUNDS ON CARBOHYDRATE METABOLISM AND ON DIABETES

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Several facts discovered during this century indicate a relation between sulphur compounds and the metabolism of carbohydrates. These are: 1, the presence of sulphur in insulin; 2, the role of cystine, cysteine, and methionine in many metabolic processes; 3, the existence of sulfhydryl groups as necessary constituents of some fundamental enzymatic systems; 4, the discovery of glutathione; 5, the selective destructive action of alloxan on the SH groups and on the beta cells of the islets of Langerhans; and 6, the action of various sulphur-containing substances on carbohydrate metabolism and on diabetes.

The sulphur content of the pancreas and insulin. Insulin contains a large quantity of sulphur (3.31%), all of which is found in the form of cystine, which constitutes 12% of the total hormone weight[52,101]. Many reducing agents which act upon the —S—S— group inactivate insulin[42,52].

The pancreas is rather rich in glutathione, although its glutathione content is lower than that of the liver, adrenal, spleen, or kidney[1,7,9,11,20]. It has been claimed that the venous blood of the pancreas contains more total neutral sulphur than the arterial blood entering the organ[76].

The large amount of sulphur in insulin, and the selective injurious action of alloxan upon the beta cells of the pancreatic islets suggest that the SH groups are a part of a fundamental (and vital) enzymatic system in these cells, and may be concerned in the production of insulin.

The action of insulin upon the SH groups of the organism. The injection of insulin produces an increase in the glutathione content of liver and muscle[20,90,100], and of heart and muscle[102]. An increase of this substance in the blood of the rabbit[3,18], the dog[106,107], and man[77] has also been observed. This increase is independent of the blood sugar level since it appears later than the hypoglycemia, and persists after the blood sugar level has returned to normal; the increase of glutathione is in direct proportion to the dose of insulin administered[106,107].

The action of Alloxan on the SH group of enzymatic systems. Alloxan is an oxidative agent[95,105] with a special affinity for the free sulfhydryl groups of

tissues[56,65]. It stains proteins a bright red color; the intensity is proportional to their SH content[56,65].

Due to its intense action upon the free SH groups, alloxan inactivates many enzymes which need SH groups for their activity. Thus, it reversibly inactivates papaine and cathepsin[85], succinodehydrase[38], triosephosphatedehydrase[86,87], the dehydrase of glyceric aldehyde[87], the enzymes which form the Robison ester, and in higher concentration, also, those which form the Cori ester[63], various enzymes involved in the metabolism of carbohydrates[6] and fats[93], the alkaline phosphatase of the kidney[73], and the enzymes involved in hepatic glucogenolysis[45]. The enzymes are reactivated, not completely in some cases, by the addition of cysteine or glutathione[38,63,85,87].

VARIATIONS OF SH CONTENT OF BLOOD AND TISSUES IN EXPERIMENTAL DIABETES AND BY ACTION OF SULPHUR COMPOUNDS. The injection of alloxan into rabbits[29,62] and rats[14] produces an immediate decrease in the blood glutathione; it also causes a decrease in the blood ergothionine[62]. Following the decrease the blood glutathione slowly rises until it reaches its initial level, 24 hours later[14].

Ten minutes after the injecton of alloxan a decrease in the hepatic (17%) and intestinal glutathione (42%) has been observed in the few animals that have been studied[28]. In rats, this diminution of glutathione content was not found immediately, nor within 4 to 11 minutes[14] after the injection of alloxan. It was normal 24 hours after the alloxan injection[48].

When a very severe diabetes is produced, a decrease in the SH content of liver and kidney is found 48 hours and 19 days after the alloxan injection[48]. This variation in the SH content of liver and kidney is not seen in the diabetes observed in rats 4 to 6 months after partial pancreatectomy (95%), but there is a striking diminution in SH content of these tissues if the rats have a severe diabetes following total pancreatectomy[48]. In all cases in which a decrease in tissue SH content has been found, the diabetes was very severe, whether it was produced by total pancreatectomy or by alloxan.

In the pancreatectomized diabetic dog a decrease in the glutathione content of the skeletal muscles, liver, and some other tissues, has been observed[8,10,20]. Some have reported a decrease in the blood[20], others an increase[79].

In human diabetes a decrease in glutathione has been observed although it does not seem to be constant, and it bears no relation to the blood sugar level[2,4,19,20,22,53,55,80,97,99]; one investigator has not been able to detect any variation[5], and in only one publication was an increase of glutathione reported[79].

The daily administration of thiouracil for 20 to 30 days caused an increase in the SH content of liver and kidney of normal and diabetic rats[48], and of thyroidectomized rats[47]. The SH content of muscle, heart, testicles, and pancreas did not show significant variations. Whether the SH content of the islets of Langerhans is affected by this procedure has not been studied as yet.

A decrease in the SH content of the tissues due to alloxan injections was of a lesser degree in rats which had been previously treated with thiouracil and thereby had become resistant to alloxan than in rats which had not received the thiouracil treatment, and thus became diabetic due to the alloxan.

PROTECTION AGAINST ALLOXAN BY TREATMENT WITH SH COMPOUNDS. Lazarow[57,58,59,60] has shown that high doses of cysteine (7.5 mM. (millimols) per kg.), glutathione (7.5 mM. per kg.) or thioglycolic acid[58] have a protective action against the intraperitoneal or

intravenous injection of alloxan, if given almost simultaneously. In this case diabetes does not develop and there is little or no damage to the beta cells of the islets. These substances protect if given immediately before the intravenous injection of alloxan, but the protection is less complete if they are injected 1 to 2 minutes after the alloxan, and there is no protection whatsoever if they are given 3 or more minutes after the alloxan. Smaller doses of glutathione[62] or cysteine[103,104] have not shown any protective action.

Cysteine (2.5 to 7.5 mM. per kg.) gives complete protection to the islets against the hyperglycemic action of alloxan, although it increases the frequency with which severe liver necrosis is produced[78]. According to Abderhalden[1], alloxan combines with cysteine in the tissues to form alloxantine and cystine; furthermore, homogentisic acid, *p*— oxyphenylpyruvic acid, and cystine are excreted in the urine, these substances being responsible for the severe liver injury.

The action of alloxan seems to be due to the fact that it inactivates the SH groups of the enzymes of the beta cells; this reaction is usually irreversible. Lazarow and Patterson[60b] state that the protective action of the SH compounds against the immediate action of alloxan is due to 3 mechanisms: 1, alloxan is reduced to dialuric acid by the SH containing compounds; although this reaction is normally reversible its reversibility is inhibited by the presence of cysteine; 2, glutathione combines with alloxan giving a compound, R-S-alloxan (maximum absorpton at 305 γ). This is the reason that the action of alloxan is not abolished when the SH substances are injected intravenously 5 minutes later; 3, alloxan and dialuric acid undergo decomposition. Since the liver has an enzyme that transforms uric acid into dialuric acid, which in turn could be changed into alloxan, it might be suspected that alloxan could be formed in man in such a manner and cause a lesion of the beta cells and thus produce diabetes.

Saviano, Leone, and de Francisis[92] have observed totally different findings in the pigeon, namely, that previous cysteine injection not only does not protect against alloxan, but causes an increase in its toxic action. Furthermore, the increased uric acid in the blood (200 mg. per 100 cc.) and the hyperglycemia (660 mg. per 100 cc.) produced were much more intense than those produced by alloxan alone.

According to Weinglass, Frame, and Williams[104], intravenous injecton of sodium bisulphite (80 to 130 mg. per kg.) immediately before alloxan injection (150 mg. per kg.) prevented the development of the fatal initial hypoglycemia and intense necrosis of the pancreatic islets in 8 out of 13 rabbits. In doses of 100 mg. per kg., the bisulphite also prevented the hypertensive action of an intravenous injection of alloxan.

In rats, the intravenous injection of BAL (British Anti-Lewisite) 2.3 dimercaptopropanol (0.36 to 0.72 mg. per kg.), shows a protective influence against the intravenous injection of alloxan (40 mg. per kg.). Certain conditions such as fasting or the administraton of ascorbic acid, which causes a decrease in the free SH content of tissues, increase the sensitivity of the animal to the diabetogenic action of alloxan and related compounds[26,60,98]. BAL has a protective action when given either by the oral or the subcutaneous route; when given intravenously it may protect for as long as 85 minutes and it reduces to a half the lethal effect of alloxan[26]. We have observed the protective action of BAL within 30 minutes of its administration[47]. BAL also protects dogs[35] and rabbits[28] against the diabetogenic

action of an intravenous injection of alloxan.

Methionine has a slightly protective effect when injected intravenously one minute before the injection of alloxan, but there is no effect if 5 minutes are allowed to elapse between injections[47]. A few preliminary experiments with sodium methanal sulphoxylate (Rongalite) showed this substance to possess no protective influence.

Recently, Siliprandi and Siliprandi[92b] have published some very striking results. Using a chemical method for determining the alloxan content, they found that both glutathione and cysteine delay the destruction of alloxan, *in vitro* as well as *in vivo*.

ANTAGONISTIC ACTION OF OTHER SUBSTANCES. The similarity between alloxan and the pyrimidines has raised the question whether a pyrimidine, ureide, or hydantoin might prevent the action of alloxan by a competition for substrate.

The intraperitoneal injection of pentosenucleotides extracted from yeast, 30 to 45 minutes before an injection of alloxan (40 mg. per kg.), affords a protection against its hyperglycemic and toxic effects[30]. The protection is still present 1 to 2 hours after the pentosenucleotide injection, but has disappeared by the end of 24 hours. By the intravenous route there is protection over a period of 30 to 120 minutes, but it is less effective.

We have not been able to obtain any protection against alloxan by treatment with uracil or thymine or pentosenucleotides, in either acute or prolonged experiments.

The protection can also be obtained by: *a*, vasoconstriction of the pancreas produced by the injection of adrenalin[54] or compression of the pedicle of the kidney or spleen[47]; *b*, nicotinic acid[4b]; *c*, other substances.

THE ACTION OF SULPHUR COMPOUNDS ON THE BLOOD SUGAR AND ON GLYCOGEN STORED IN NORMAL AND DIABETIC ANIMALS. There have been various reports that the administration of sulphur causes a decrease in blood sugar level, an increase in glycogen, and a diminution in metabolism. Sulphur was administered by the oral, muscular, or subcutaneous route in the form of colloidal sulphur, or an alcoholic or glycero-alcoholic solution of sulphur, or by inunction of sulphur on the skin.

In rabbits, a decrease in blood sugar level after the administration of small doses of sulphur has been reported; in some experiments the decrease was more noticeable after several months of continuous treatment[15,16,17,19,32,34,74,75,81,82]. Usually the decreases were of 10 to 20% of the initial value, but one paper mentions deaths caused by hypoglycemia[32]. Almost all of the investigators have observed that high doses of sulphur increase the blood sugar level[15,82], or that such doses may produce first hypoglycemia and later hyperglycemia[74,75].

Other substances such as sodium di, tri, and tetrathionate, ichthyol, cysteine, and the polythionic acids may cause a variable fall in blood sugar level[13].

When rabbits were submitted to procedures which cause an increase in blood sugar level, such as the oral or intravenous administration of glucose[9,24,74,75,82], bulbar puncture[19], injection of adrenalin[19,32,83], it was found that rabbits which had been previously treated with sulphur showed less increase in blood sugar level than the controls; and that phloridzin would produce in these animals greater hypoglycemia and less glycosuria than in those which received no sulphur treatment[20].

By administration of sulphur a decrease in blood sugar level has also been described for the normal[19,21] and the diabetic man. In the case of mild or moderately severe diabetes, a decrease in glycosuria, ketonuria, glycemia dur-

ing fasting, and an increase in tolerance and alkaline reserve have also been observed[15,16,17,19,21,31,88]. Similar results have been obtained when patients are exposed to baths or the injection of sulphurous mineral waters[15,27]. However, many negative results have been described with sulphur preparations[33, 37,96]; or an increase has been observed in sympathiocotonic and a decrease in vagotonic persons[33]. In some papers no decreases have been reported, and sometimes an increase in blood sugar level has been obtained[64,83]. Due to this variability and to the lack of detailed and satisfactory case histories, and, above all, because of the more definite activity of insulin, this therapeutic measure is used in only a few places, and in a very limited form.

Recently, favorable results have been described in the treatment of rabbits having alloxan diabetes with sulphurous waters[84].

A net increase in hepatic glycogen has been observed by means of histological or chemical methods in rabbits[15,16,17,19,32,34,74,75,89] and rats[15,34] after they have received a prolonged administration of sulphur by mouth or injection.

The repeated intravenous injection of S-methylthiourea in dogs and cats produced an increase of glycogen in the liver; such glycogen was not very soluble in water and was resistant to glycogenolysis. This has been compared to the glycogen accumulation observed in Von Gierke's disease[50]. The administration of thiourea also produced a marked increase in hepatic glycogen[72]. A lowered metabolic rate has been observed in rabbits which have received a prolonged treatment with sulphur[15, 19]; this did not become apparent in anesthetized rabbits[82]. Prolonged sulphur treatments also caused hyperplasia of the adrenal glands[32].

Action of Sulphur Compounds on Insulin Secretion. The hypoglycemic action of sulphur has not been observed in totally pancreatectomized dogs, but it has been studied in partially pancreatectomized animals[19]; a few workers have observed very small diminutions of the hyperglycemia when sulphur was given after total pancreatectomy. The hypoglycemic action has not been observed in rabbits after the vagi have been severed[75]. These facts suggest that the hypoglycemic effect might be due to a secretion of insulin brought about by a vago-pancreatic mechanism.

Ruiz, Silva, and Libenson[91] have found that 4 or 5 methlythiolimidazole, administered by oral or intravenous route, had a marked hypoglycemic effect in the rabbit, the blood sugar level being lowered by 13 to 30% of the initial value. Several compounds such as 4 or 5-amino-methyl-2-thiol-imidazole, 4 or 5-glucil-2-thiol-imidazole,* 2-thiol-imidazole, cyclo-decamethylenthiourea and others were found to be inactive. Ethylthiourea, thiophenol, and thioacetic acid were found to be slightly active.

In 1942, Janbon[51] found unexpectedly that para-aminobenzene-sulphamido-isoproppyl-thiodiazol (2254 RP) produced a definite decrease in the blood sugar level. If this is given to undernourished men that do not receive a previous glucose treatment, hypoglycemic coma may occur.

Loubatières[66,67,68] confirmed this effect in dogs. He observed hypoglycemia after oral or intravenous administration of this substance (0.1 to 0.4 gm. per kg.); if the administration is repeated for several days there occur convulsive seizures and irreversible nervous alterations, notwithstanding the administration of glucose. This hypoglycemic action is

* The formula so designated by them corresponds to tetryl-2-thiol-imidazole.

due to a stimulation of insulin secretion, through the direct action of this sulfamide upon the beta cells of the islets of Langerhans. Thus, the hypoglycemic action is not obtained in totally pancreatectomized dogs, but is manifested in partially pancreatectomized dogs which have retained 1/6 of the pancreas. Even when only 1/100 of the pancreas is retained, and this fraction is found around the duct of Wirsung, some of the hypoglycemic action is apparent. With the technique of Zunz and LaBarre insulin secretion can be demonstrated by a pancreatic-jugular anastamosis, joining the duodenopancreatic vein of a donor dog injected with the 2254 RP to the jugular vein of a dog with alloxan diabetes. A low blood sugar level (30% decrease) was also seen when a weak dose (0.04 gm. per kg.) of the drug was injected directly into the afferent artery of the tail of the pancreas. The hypoglycemia was very severe (the blood sugar level was decreased by 68%) when a small dose (0.05 gm. per kg.) injected into the Wirsung canal remained in contact with the pancreatic gland.

Furthermore, this substance allows the accumulation of large quantities of glycogen (10 times the original amount) in a dog which has been fasting for several days. This substance does not increase the RQ of a totally pancreatectomized dog, showing that its action is not direct but through its stimulation of the secretion of insulin. This drug does not inhibit the diabetogenic action of the anterior lobe of the hypophysis as its administration does not prevent the development in the usual time and intensity of the diabetes induced in the dog by injections of fresh anterior pituitary extracts.

La Barre and Reuse[54b] have confirmed the finding that the intravenous injection of 2254 RP (in doses of 120 mg. per kg.) causes a marked decrease of the blood sugar level. This decrease is at its peak 1 to 1½ hours after the injection, the blood sugar level being restored to normal within 3 to 4 hours. The fall of the blood sugar level induced by this drug is greater and lasts longer after bilateral adrenalectomy. The hypoglycemic reaction of 2254 RP does not appear if the animal has diabetes produced by a previous administration of alloxan (50 to 150 mg. per kg.). This suggests that the action of the substance rests on a direct stimulation of the endocrine secretion of the pancreatic islets.

Bovet and Dubost[12] and Loubatières[66,67,68] have studied in rabbits and dogs the hypoglycemic effect of various compounds and have proved that the amino-thiazoles lacking the sulfanilamide group do not have a hypoglycemic action. All the substances which produce hypoglycemia belong to the *p*-amino-benzene-sulfanilamide-thiodiazol group. Among them the most active compounds are the butyl, amyl, isoamyl, propyl, and isopropyl derivatives. The methyl and ethyl derivatives show no action whatsoever and the hexyl, heptyl and aminothiodiazol derivatives show only a negligible effect. Benzene-sulfanilamide-isopropyl-thiodiazol, which differs from 2254 RP only in that there is no amide group joining the aromatic group, has also been found to be inactive. Therefore, according to Loubatières, the hypoglycemic action is related to the *p*-amino - benzene - sulfanilamide - thiodiazol molecule, the lateral chain joined with the thiodiazol nucleus playing a very important part.

A hypoglycemic action is produced by the isopropyl, butyl and amyl alcohols, but not by the methyl and ethyl alcohols. The activity is greater when the 3 former compounds are combined with the *p*-amino-benzene-sulfamide-thiodiazole. Loubatières thinks that the

effect of these compounds results from the thiodiazole nucleus being reinforced by the action of the remaining parts of the molecule.

Chen, Anderson, and Maze[25] have studied a similar substance, 2-sulfanilamide-5-cyclopropyl-1, 3, 4-thiodiazole, which has a chemotherapeutic action upon certain bacteria. This compound is only slightly toxic in rabbits, but when administered for a long period of time in rats it induces goiter formation. When given orally to the normal rat, it causes a fall in the blood sugar level, to 48 to 52 mg. per 100 cc; on the other hand, when given to rabbits with alloxan diabetes, the blood sugar level does not fall but rises to very high values (650 mg. per 100 ml.). They conclude that this substance stimulates the insulin secretion of the pancreas.

The Action of Sulphur Compounds Upon the Sensitivity to Insulin. Candela, Gascon, and Panigua[23] have observed that after thiouracil treatment totally pancreatectomized dogs require a smaller insulin dosage.

Treatment for 30 days with methylthiouracil increased the sensitivity to insulin in normal rabbits[2b] and in those with alloxan diabetes[26b]. Thyroxine appeared to have the opposite effect, but it was not clear cut when the rabbits had received a previous treatment with thiouracil.

It has been asserted that dithioglycolic acid sensitizes the rabbits to the action of insulin[36]. In human diabetes, sulphur treatments reinforced the action of insulin only in half of the cases; this treatment was not very useful in clinical practice[64].

Preventive and Curative Action of Sulphur Compounds in Experimental Diabetes. The fact that thyroidectomy in rats decreased the frequency of alloxan diabetes[39,40,41,43,49,70,71] and also the frequency of diabetes resulting from the resection of 95% of the pancreas[39,40,41,43,44,71] led to the investigation of whether thiouracil had any similar preventive or curative action.

Alloxan diabetes. It has been shown that the administration of thiouracil (200 mg. per kg. per day) to normal rats during periods of 12, 20 and 30 days, produces a marked increase in resistance to the diabetogenic and toxic

TABLE 1.—PREVENTIVE ACTION OF ORALLY ADMINISTERED THIOURACIL AGAINST THE INTRAVENOUS INJECTION OF ALLOXAN IN WHITE MALE RATS

*Thiouracil treatment**	*Number of Rats*	*Mortality*		
		Alloxan 50 mg./kg.	*Alloxan 75 mg./kg.*	*Alloxan 100 mg./kg.*
Controls, none	10	60%	100%	100%
2½ hours before alloxan	6	—	—	100%
24 hours before alloxan	6	—	100%	100%
12 days daily	10	20%	60%	—
30 days daily	10	0	0	40%

* Thiouracil given orally, 200 to 300 mg. per kg. body weight.

TABLE 2.—SENSITIVITY OF WHITE RATS TO INTRAVENOUS ALLOXAN

	Alloxan mg./kg. body weight						
	25	*35*	*50*	*75*	*100*	*125*	*150*
	Mortality percentage						
Controls	40	40	60	100	100	100	
Thyroidectomized	0	0	0	40	100	100	
Thiouracil treatment*	0	—	0	0	0	33	100

* 200 mg. per kg. body weight per day by oral administration.

action of the intravenous injection of alloxan; this protective effect has not developed 2 to 24 hours after the first thiouracil injection (Table 1). The resistance induced with thiouracil is greater than that induced by the removal of the thyroid[39,40,41,43,71] (Table 2). Also, the alloxan resistance caused by thyroidectomy is increased by treatment with thiouracil (Tables 2 and 3). This shows that this substance not only induces thyroid deficiency but that it has an extra thyroidal action as well.

After the administration of thiouracil

TABLE 3.—PREVENTIVE EFFECT OF THIOURACIL AGAINST THE ACTION OF INTRAVENOUS ALLOXAN

			Mortality with 80 mg./kg. alloxan	
	Thiouracil mg./kg./day	*Days of treatment*	*Number of rats*	*Mortality %*
Thyroidectomized*	200	20	11	18
Thyroidectomized*	0	0	19	36
Controls	0	0	7	100

* Thyroidectomy was performed 20 days before the alloxan injection.

TABLE 4.—PROTECTIVE ACTION OF CERTAIN SUBSTANCES AGAINST THE TOXICITY OF ALLOXAN IN WHITE RATS

*Substance**	*Treated* *mg./kg.*	*Days*	*Alloxan mg./kg. intravenous*	*Mortality due to alloxan* *Treated***	*Controls***
Thiouracil	200	12	50	2(10)	6(10)
		30	50	0(10)	6(10)
Cysteine Hcl	400	20	50	1(10)	7(10)
Cyclopropylthiouracil	200	20	50	2(7)	8(8)
4 Methylthiouracil	200	20	50	4(8)	8(8)
5 Methylthiouracil (thymine)	170	20	50	2(9)	7(10)
5 Ethylthiouracil	240	20	50	4(8)	8(8)
4, 5 Dihydrothiouracil	150	20	50	6(7)	8(8)
Thiourea	150	12	50	6(10)	6(10)

* Oral administration.
** Total number of animals used given in brackets.

for several days, there was an increase of the free SH groups in the kidney and liver of both normal[48] and pancreatectomized rats[47] (Table 5). In the latter group, the free SH of kidney and liver had previously been found to be increased after thyroidectomy. It is probable that this SH increase might be one of the main factors in the resistance of thyroidectomized rats against alloxan.

In the white rat, the previous daily treatments for 20 or more days of several substances (Table 4) such as: cysteine (400 mg. per kg. per day), 6-cyclo-propyl-2-thiouracil (200 mg. per kg. per day), 5-methyl-2-thiouracil (thio-thymine) (170 mg. per kg. per day), 6-methyl-2-thiouracil (200 mg. per kg. per day), 5-ethyl-2-thiouracil (240 mg. per kg. per day), and 2-thiohydrouracil (150 mg. per kg. per day), also increase the resistance to alloxan. The action of thiourea (150 mg. per kg. per day) and sodium thioglycolate (170 mg. per kg. per day) was questionable.

The inactivity of cysteine (300 mg. per kg. per day), methionine (200 mg. per kg. per day), sulfanilamide (250 mg. per kg. per day), sodium thiosulfate (100 to 1000 mg. per kg. per day), sodium methanal-sulfoxilate[47], sulfanilamide-cyclopropyl-thiazole and 2254 RP, was demonstrated in similar experiments.

TABLE 5.—SH CONTENT OF LIVER AND KIDNEY OF WHITE MALE RATS TREATED BY THIOURACIL OR CYSTEINE

Treatment	*Number of rats used*	*Liver SH* mg./100g average*	*Statistical value of the differences***	*Kidney SH* mg./100g.*	*Statistical value of the differences***
Normals	74	166	—	58	—
Thiouracil (20 to 30 days) 200 mg./kg./day	43	278	4.9	97	8.1
Thiouracil (30 days) 200 mg./kg./day, discontinued 30 to 52 hours before	6	243	4.5	91	3.9
Thiouracil (30 days) 200 mg./kg./day, discontinued 96 hours before	4	185	—	78	—
Methionine (30 days) 250 mg./kg./day	6	167	—	57	—
Thiothymine (20 days) 170 mg./kg./day	4	252	—	108	—
Cysteine (20 days) 400 mg./kg./day	9	220	4.1	95	6.9
Cyclopropylthiouracil (20 days) 200 mg./kg./day	6	364	19.0	102	6.6
Thyroidectomized (20 days)	19	243	6.9	75	2.5
Thyroidectomized, treated by thiouracil (20 days) 200 mg./kg./day	6	334	14.3	141	10.3

* SH content calculated as reduced glutathione

** According to the formula $\frac{\text{Average}_1 - \text{Average}_2}{\sqrt{\sigma AV_1 + \sigma\ Av_2\ \sigma}}$

TABLE 6.—CURATIVE ACTION OF THIOURACIL ON THE PERMANENT DIABETES OF THE ALBINO RAT

	Controls (no thiouracil)		*Thiouracil treated*	
*No. days thiouracil treatment**	*Mortality after alloxan***	*Incidence of diabetes***	*Mortality after alloxan***	*Incidence of diabetes***
16	0 (7)	7 (7)	0 (9)	9 (9)
26	2 (7)	5 (5)	1 (9)	5 (8)
34	2 (7)	5 (5)	1 (9)	4 (8)
39	2 (7)	5 (5)	2 (9)	2 (7)

* Oral administration of thiouracil (200 mg. per kg. per day) started 16 days after alloxan.

** Number of animals in brackets.

Thiouracil had a curative effect on rats suffering from moderately severe alloxan diabetes (Table 6). The curative action was not apparent in very severe diabetic cases of rapid evolution. Uriage's sulphurous mineral water had a favorable action upon the alloxan diabetes of rabbits[84].

Diabetes in Rats with Subtotal Pancreatectomy. Daily treatment with thiouracil (200 to 400 mg. per kg. per day) delayed the appearance and decreased the frequency of diabetes in rats in which 95% of the pancreas had been resected, as compared to the untreated ones[71]. The same treatment had a curative effect in a certain number of subtotally pancreatectomized rats with a moderate diabetes.

The daily oral administration of cysteine (400 mg. per kg. per day) and thiothymine (170 mg. per day) had an appreciable preventive influence on the development of diabetes[47]. BAL and other compounds were ineffective[47]. Continuous thiouracil treatments induced, in cases of very severe diabetes, a very short transitory improvement[47].

Normal Rats with Fat Diets. Diets rich in pork and beef fat increased markedly the sensitivity of rats to the diabetogenic and toxic action of alloxan[71]. This sensitivity disappeared if the rats received thiouracil simultaneously with alloxan[46,71].

Pancreatectomized Rats with Fat Diets. The administration of thiouracil largely diminished the harmful action of the high fat diet on the diabetes caused by subtotal pancreatectomy[46,47].

Condition of the Pancreas. In rats protected by all the substances which have been previously mentioned, there are fewer lesions of the beta cells of the islets of Langerhans than in those which receive no protective treatment. Upon histological examination, it was seen that generally the islet tissue had not increased, although no measurement of such tissue was made.

Diabetic Dogs. Candela, Gascon, and Paniagua[23] have treated totally pancreatectomized diabetic dogs receiving 1 unit per kg. per day of insulin with thiouracil (10 to 20 mg. per kg. per day). At the beginning, irregular variations of the blood sugar level were observed; 10 to 15 days later increased tolerance to carbohydrates and hypoglycemia was evident, making it necessary to reduce the daily insulin dose.

In dogs having moderately severe alloxan diabetes and receiving no insulin treatment, the administration of thiouracil induces a decrease in blood sugar level. In very severe alloxan diabetes treated daily with globin-insulin, the administration of thiouracil lowered the blood sugar level and the dose of insulin had to be reduced.

Tissue SH Groups. The treatment with thiouracil, other thiouracils and cysteine, for 20 to 30 days, produced an increase of free SH in liver and kidney of normal and pancreatectomized rats (Table 5)[47,48,71a]. In severe alloxan or pancreatic diabetes there is a decrease of free SH[48] in the tissues.

THE DECREASE IN SH GROUPS AND THE PRODUCTION OF DIABETES. The decrease in SH groups seems to favor the appearance of diabetes under different conditions.

Alloxan Diabetes. Different procedures which decrease the free SH of tissues produce an increase in sensitivity to the diabetogenic action of alloxan. Such procedures are: fasting, low protein diet, chloroform, high fat diet and hyperthyroidism.

Inversely when the free SH content is increased there occurs an increase in resistance to alloxan. This follows treatment with thiouracil and cysteine or thyroidectomy. These 3 procedures also decrease the frequency of the diabetes which appears after subtotal pancreatectomy in rats (removal of 95% of the pancreas).

Uric Acid Diabetes. Griffiths[35,35a] injected uric acid (1 gm. per kg. intraperitoneally) into rabbits maintained on methionine and cysteine deficient diets and in which blood glutathione decreased from 38 to 18-23 mg. %. There occurred an initial hyperglycemia during 8 hours. After 24 hours blood sugar was normal. Between 24 and 48 hours blood sugar increased and remained high with the usual diet plus alfalfa. They remained hyperglycemic and glycosuric 4 to 5 days and then became normal. A similar effect was produced by alloxan in rabbits with the usual diet.

By adding 0.2% methionine to the deficient diet the reduced glutathione remained at 30 mg.% and the injection of uric acid produced the initial blood sugar increase but the secondary increase did not appear.

Diabetes Produced by Adrenocorticotrophin. Recently Conn *et al.*[26a,b,c,d,e] have produced in 4 men (3 normal, 1 with gout) a metabolic change similar to diabetes mellitus by the daily injection of adrenocorticotrophin during several days. The diabetic symptoms observed were: 1, glycosuria; 2, increase in blood sugar; 3, a typical diabetic tolerance curve. These symptoms disappeared after discontinuing the treatment with adrenocorticotrophin. There occurred in addition; 4, a relative increase in resistance to insulin; 5, in some cases an increased excretion of nitrogen in urine; 6, an increase in urinary uric acid; 7, a decrease in blood glutathione (25 to 50%).

The appearance and persistence of glycosuria corresponded well with the excretion of uric acid and with the decrease in blood glutathione. Conn *et al.* suppose: 1, that adrenocorticotrophin produces an increase in uric acid and related purines in cells and that some of these substances injure the beta cells of the islets as does alloxan; 2, that the decrease in glutathione and perhaps other SH containing substances would alter the functional activity of the beta cells and would make them more sensitive to the injuring factor and to hyperglycemia; 3, that adrenocorticotrophin decreases the capacity of the organism to utilize carbohydrates of any origin; 4, a decrease of the renal threshold for glucose by functional alteration of the renal tubuli. These actions would be related to the decrease in the SH groups which are necessary for the cellular enzymes and for the reabsorption by the renal tubuli.

In one of the patients after the fourth daily injection of adrenocorticotrophin the injection of glutathione produced a transitory (1 to 2 hours)

normalization of blood sugar and a disappearance of the glycosuria during 1 hour. Conn *et al.* suppose that glutathione improved the action of the cellular enzymes which require SH groups for their action[26b].

Discussion. MECHANISM OF ALLOXAN ACTION UPON THE ISLETS. Alloxan produces a selective lesion (coagulation necrosis, for instance), of the beta cells of the islets of Langerhans of the pancreas. The internal mechanism producing this lesion has not been elucidated as yet. It is probably due to a generally irreversible metabolic alteration of the beta cells caused by alloxan. Regarding the nature of this alteration, several hypotheses may be formulated. The first one is that there is a competition between alloxan and a similar substance necessary for the function of the cells. The inactivity of uracil and thymine is evidence against this theory. Another possibility is that there is a selective accumulation of alloxan in the beta cells, with the result that these cells are subjected to greater damage than the others. However, there is no direct evidence to date of this accumulation. The third hypothesis is that alloxan inactivates the SH groups, which are of particular importance to the life and function of the enzymatic systems of the beta cells. The well known disturbing action of alloxan upon the SH of protein and various cellular enzymes is evidence in favor of this theory. This hypothesis has not yet been definitely validated since the SH values of the beta cells before and after the alloxan action are not known. The protection against alloxan furnished by substances which produce an increase of tissue SH gives weight to this theory. However, it is not known whether these substances have a protective action directly on the islets or on other tissues (liver, for instance). The high amount of sulphur in insulin is another, even though an indirect, argument in favor of the importance of sulphur in the function of the beta cells.

PROTECTION AGAINST ALLOXAN. Several substances having free SH groups, such as cysteine, glutathione and BAL, administered intravenously in high doses, neutralize (completely or partially) the toxic and diabetogenic action of alloxan, if injected immediately before administration of alloxan. This is a case of chemical neutralization of alloxan, probably occurring in the blood. The injection of alloxan causes, in untreated animals, an immediate fall of the normal blood glutathione. The immediate slight and temporary protective action of methionine and some amino acids appears to be due to a direct combination with alloxan. The immediate previous protective action of adrenalin[54] and several surgical operations[47] seems to be due to pancreatic vasoconstriction causing a probable diminution of the alloxan-containing blood reaching the islets.

In animals treated for 20 to 30 days with substance that increase the SH groups in the tissues but not in the blood, it is probable that the alloxan is destroyed by such tissue SH or that these SH groups afford a protection to the cells. The protective action cannot be ascribed to the pyrimidine nucleus which is lacking in sulphur, since uracil, thymine and the pentose nucleotides are ineffective. This protection is specific of only certain sulphur compounds since sulfanilamide, thiosulfate, methionine and thioglycolic acid are ineffective.

Thyroidectomy increases tissue SH and also the resistance to alloxan, and thiouracil treatment reinforces even more so the SH concentration and the resistance to alloxan. On the other hand, other procedures, such as fasting[54], ascorbic acid and, above all, diets deficient in cysteine, methionine

and protein[61,69], decrease the tissue SH and increase the sensitivity to the diabetogenic effect of alloxan.

PREVENTION AND RECOVERY OF DIABETES. In subtotally pancreatectomized rats (95% of the pancreas removed), there is a delay in the development and a decrease in the frequency of diabetes if the animals are treated daily over a period of several months with substances that increase the tissue free SH (thiouracil, thiothymine and cysteine) as compared to subtotally pancreatectomized non-treated rats. In very severe diabetes induced by pancreatectomy or by alloxan, there is a sharp decrease in the SH of kidney and liver. The previous treatment with substances which increase the SH of such tissues furnishes a marked protection against diabetes. This treatment has a curative action when applied to rats developing a moderate diabetes after subtotal pancreatectomy. In all these cases the treatment produces an increase of the SH groups which were reduced under the influence of the disease. In the successfully treated animals the beta cells of the islets of Langerhans either show little damage or are in very good condition. Hypertrophy or hyperplasia of the islets has not been observed, although their occurrence cannot be ruled out since no precise measurements have been made in such tissues.

Summary. The insulin which is produced by the beta cells of the islets of Langerhans of the pancreas contains a large quantity of sulphur. The SH groups seem to be very important for the proper function of the beta cells. Alloxan specifically alters the free SH of several tissues, and impairs many of the tissues. In some tissues the alteration is only temporary but it is usually irreversible in the beta cells. As a result of this change a permanent diabetes develops. Alloxan is an oxidizing agent specifically acting on SH, and many of those enzymes which need the SH groups for their functioning are inactivated because of the intense effect of alloxan upon the SH groups. In some instances, the addition of cysteine or glutathione produces a partial protection. The injection of insulin usually produces some increase of the free SH content of certain organs and of the glutathione.

A decrease of the free SH of many organs is seen in cases of very severe diabetes. In human diabetes a decrease in the blood glutathione has been observed, although this bears no constant relationship with the blood sugar level.

When the thiouracils or cysteine are administered the free SH content of many tissues increases. In the rat, these substances produce a diminution of the frequency of the diabetes which appears some months after almost total pancreatectomy (95%).

Cysteine, glutathione and some SH bearing compounds have a protective influence against the diabetogenic action of alloxan if given almost simultaneously, but there is no protection if they are injected more than 2 minutes before the alloxan.

In some species of animals, especially in the rabbit, the administration of adequate doses of sulphur produces a decrease of the blood sugar level and an increase in the liver glycogen.

In some cases, it has been found that other sulphur compounds also have the capacity of decreasing the blood sugar level. It has been claimed that a similar result has been obtained in cases of mild diabetes by the ingestion, or baths, of sulphurous mineral waters.

Some sulfanilamide-thiodiazol compounds, especially 2254 RP, produce a definite decrease of the blood sugar level, but only if the pancreas is present. This is due presumably to a stimulation of the islets of Langerhans and

the correspondent increase of insulin secretion.

Certain procedures such as thyroidectomy or prolonged treatment with thiouracil or cysteine which increase the free SH groups of tissues markedly increase the resistance to the diabetogenic action of alloxan. They also diminish the incidence of diabetes after subtotal pancreatectomy in the rat and can even produce permanent cures in a certain percentage of mild diabetic animals. Treatment with thiouracil or cysteine also counteracts the increased sensitivity to alloxan produced in rats under fat diets.

The study of the functional importance of glutathione and SH in relation to cellular metabolism and to the functional disturbance and treatment of diabetes deserves special attention and research.

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CAPILLARY FRAGILITY STUDIES IN DIABETES MELLITUS AND THE USE OF RUTIN IN DIABETIC RETINITIS

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Although rutin has been used clinically since 1942, its effectiveness remains open to question. It is said to decrease both capillary fragility and permeability and for this reason has been used in diabetic and hypertensive retinopathy. Both of these conditions are associated with a high incidence of increased capillary fragility. As an indication of the importance of retinopathy in diabetes may be cited the findings of Waite and Beetham[11], who in 1935 reported an incidence of 18% in 2002 diabetic patients. White and Waskow[12] found retinitis in 75% of 220 juvenile diabetics (patients with onset of diabetes at 15.0 years of age or under) who had had the disease for 20 years or more.

The conflicting reports on the value of rutin in the treatment of retinopathy have been summarized recently by Hollenhorst and Wagener[4]. Donegan and Thomas[2] treated 110 diabetic subjects with an average daily dose of 150 mg. of rutin and stated that "although no significant improvement in vision or decrease in retinopathy was observed in diabetes after rutin therapy it may be significant that no loss of vision or increase in retinopathy occurred during a period of 10 to 12 months treatment." Rodriquez and Root[8] treated 20 diabetic patients with retinitis and increased capillary fragility and found that the latter returned to normal or borderline levels in 5 cases but in no patient was improvement in retinitis seen. Givner[3] noted that several patients had retinal hemorrhages during the course of rutin therapy. Dolger[1] stated that he had given up the use of such substances as Vitamin P and C, rutin and hesperidin because the results were not strikingly different from those in a control group. White[13] has stated that it is her clinical impression that the progress of retinitis in juvenile diabetics has been less rapid in those who have used rutin.

It is the purpose of this paper to present the results of further studies on the strength of capillaries in diabetes mellitus and to note the effect of rutin therapy on increased capillary fragility and diabetic retinitis.

Subject and Methods. Most of the methods described for measuring the strength of the skin capillaries can be classified as positive or negative pressure tests. The ease with which the petechiae can be produced by either method is taken as a measure of the strength of the capillaries. Many methods have been described and are summarized by Munroe, Lazarus and Bell[5]. In the technique of Göthlin, which has been used most extensively, 35 mm. of mercury pressure for 15 minutes is used and the petechiae counted in a 6 cm. circle in the antecubital fossa. After an hour the test is repeated using 50 mm. pressure. The petechial index is calculated by adding twice the number of petechiae obtained in the first stage to the number produced in the second. An index of 8 or less is considered normal and one of 13 or greater, abnormal. Wright and Lilienfeld[14]

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held the pressure at midway between systolic and diastolic levels and recorded as abnormal more than 20 petechiae in a 2.5 cm. circle, 4 cm. below the crease of the elbow on the anterior aspect of the forearm. Reid[6] used 80 mm. of mercury pressure for 5 minutes and counted the petechiae in a 2.5 cm. circle at the elbow and wrist. More than 14 at the elbow or 3 at the wrist were considered abnormal.

In the present study the Göthlin technique was not used because of the time involved in doing the test. Methods in which the pressure is maintained midway between systolic and diastolic levels were not used because of pain frequently caused by the higher pressure and because of the possibility of producing a vascular thrombosis. A technique was standardized on a group of 50 non-hypertensive, non-diabetic persons, both male and female ranging in age from 18 to 76 years (average 44.6 years). This group was made up of 40 patients on the wards of the Peter Bent Brigham Hospital and 10 members of the staff of the George F. Baker Clinic who had no evidence of nutritional deficiency, blood dyscrasia, hypertension or diabetes. The following technique was used: A blood pressure cuff was applied to the upper arm and pressure maintained at 80 mm. of mercury for 4 minutes. The petechiae were counted in a 6 cm. circle on the flexor surface of the forearm in an area in which there seemed to be the most petechiae. The petechiae were counted, using a hand lens and a bright light. Other authors have used a definite area on the forearm mapped out prior to applying the pressure. In our cases the circle was drawn in the area which contained the most petechiae regardless of its location on the surface of the forearm. It was observed repeatedly that often there would be few or no petechiae just below the antecubital fossa and at the same time there might be many at the wrist or *vice versa*. In this control group 42 showed a petechial count between 0 and 10, while 5 had a count between 10 and 20; in only 3 cases was the count over 20. From this control group, therefore, it was concluded that with this method a count of over 20 petechiae was definitely abnormal.

We studied 220 patients at the George F. Baker Clinic. The following data were recorded on each patient: Age at onset of diabetes, present age, duration of diabetes, weight, insulin dose, blood pressure, results of funduscopic examination and capillary fragility. From these data patients were divided into 4 main groups: 1, those with diabetic retinitis and increased capillary fragility; 2, those with retinitis and normal capillary fragility; 3, those without retinitis but with increased capillary fragility; and 4, those with no retinitis and normal capillary fragility. These 4 groups were also classified as to whether or not hypertension was present. The patient was regarded as having hypertension if the systolic pressure was over 150 mm. or the diastolic over 90 mm. of mercury. In 38 of the 220 patients observations were made on the effect of rutin on capillary fragility and retinitis.

TABLE 1.—INCIDENCE OF RETINITIS AND CAPILLARY FRAGILITY IN DIABETIC PATIENTS WITH AND WITHOUT HYPERTENSION

Groups	*No. Cases*	*Patients with Hypertension*		*Patients without Hypertension*	
		Number	*Per cent*	*Number*	*Per cent*
Retinitis with Increased Capillary Fragility	68	45	66.1	23	33.9
Retinitis with Normal Capillary Fragility	12	4	33.3	8	66.6
No Retinitis but increased Capillary Fragility	68	30	44.1	38	55.9
No Retinitis but normal Capillary Fragility	72	24	33.3	48	66.6
Totals and Averages	220	103	46.8	117	53.2

Results. Our results are partially summarized in Tables 1 and 2. It will be noted that of the 220 patients examined, 68 had both diabetic retinitis and abnormal capillary fragility; 12 had retinitis with normal fragility. Thus, 85% of the 80 patients with retinitis had

increased capillary fragility. Of the remaining 140 patients, 68 had abnormal capillary fragility but no retinitis and 72 had both normal retinae and capillaries. Thus 48.5% of the patients without retinal pathology showed abnormally weak capillaries indicating that diabetes *per se* is associated with increased capillary fragility. This is in agreement with Rodriquez and Root[8] who found the capillary fragility to be increased in 40% of 100 unselected diabetic patients. That hypertension contributed to the high incidence of both retinitis and increased capillary fragility in our cases is shown by the fact that it is associated twice as frequently with retinitis and increased capillary fragility as with normal retinae and capillaries, 66.1%, as contrasted with 33.3%. As a corollary to this, of the 103 patients with hypertension it will be noted that 49 (47.9%), had retinitis; whereas, of the 117 cases without hypertension only 31 cases (26.4%), had retinitis. In Table 2 it will be seen that the average duration of the diabetes in the group with retinitis and increased capillary fragility was 17.2 years. In marked contrast, in the group with no retinitis and normal fragility the average duration was 10.5 years. There is very little difference in the average age of the different groups. The patients with retinitis and increased capillary fragility had the largest percentage of long duration juvenile diabetics.

Of the 80 cases with diabetic retinitis 32 were treated with rutin for a period varying from 6 weeks to 30 months with an average of 12 months. Ten patients were treated for 18 months or longer with a maximum of 30 months. An additional 6 patients without retinitis but with increased capillary fragility were also treated in an attempt to correct the fragility and thus possibly prevent retinitis. Tests of capillary fragility were done 147 times on the 38 patients. The average age of the 32 patients with retinitis was 43.3 years with an average duration of the diabetes of 19 years. Fourteen of these were patients with onset of diabetes in childhood, the majority of whom had severe retinitis proliferans, hypertension, albuminuria and peripheral arteriosclerosis. The average duration of the disease among the juveniles was 20.1 years; the shortest duration in this group was 13 years and the longest 26 years. The majority of the 32 patients with retinitis were followed both by the internist and the ophthalmologist. Hypertension was present in 53.1%. Most patients received 180 mg. of rutin a day although 10

TABLE 2.—INFLUENCE OF AGE AND DURATION OF DIABETES ON RETINITIS AND CAPILLARY FRAGILITY

Groups	*No. Cases*	*Average Age Years*	*Average Duration Diabetes Years*	*Juvenile Patients**	
				Number	*Per cent*
Retinitis with Increased Capillary Fragility	68	48.8	17.2	18	26.4
Retinitis with Normal Capillary Fragility	12	54.4	11.5	2	16.6
No Retinitis but Increased Capillary Fragility	68	53.0	11.4	5	7.3
No Retinitis and Normal Capillary Fragility	72	46.3	10.5	12	16.6

* Onset of diabetes at age 15.0 years or under.

took 300 mg. or more per day. One patient took a maximum daily dose of 1320 mg. The behavior of the capillary fragility during the period of rutin therapy was as follows: decreased to normal, 4; decreased but not to normal, 4; remained approximately the same, 13; increased, 6; fluctuated, 5. It is evident that in agreement with the experience of Rodriquez and Root[8] the capillary fragility returned to normal in only 25% of the cases. Among the 10 patients treated with rutin for 18 months or longer, in 2 the capillary fragility returned to normal, in 1 it decreased, in 1 increased, in 4 remained approximately the same, and 2 fluctuated. Thus, in only 3 of 10 cases was the capillary fragility favorably affected despite the long duration of treatment. Among the 10 patients whose dosage of rutin was increased to 300 mg. or more of rutin per day none returned to normal levels, 3 were decreased, 6 remained the same, and 2 fluctuated.

The average age of the 6 patients treated with rutin who did not have retinitis but who did have increased capillary fragility was 32 years and they had had diabetes for an average of 15.1 years. They were treated over a period varying from 4 to 12 months with an average of 7.3 months. Only 1 patient of the 6 had hypertension. In 4 of the 6 the capillary fragility returned to normal while on rutin therapy, whereas in only 1 did it increase and in 1 it remained the same. This is in agreement with the findings of

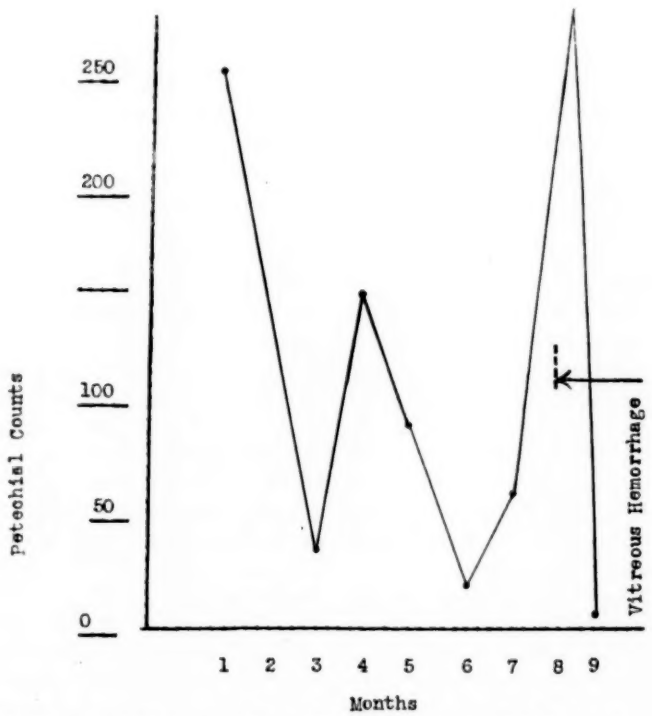

FIG. 1. Variation in petechial counts (Case 15137) over a period of 9 months while on rutin therapy (180 mg. daily, except briefly 240 mg. daily). Note occurrence of vitreous hemorrhage 3 weeks after capillary fragility had been found relatively low. The petechial count became very high subsequent to the hemorrhage.

Donegan and Thomas[2], who stated that it is easier to restore the capillary fragility to normal in diabetics without retinitis than in those with retinitis.

Five of the 32 patients with diabetic retinitis while on rutin therapy had vitreous hemorrhages severe enough to impair vision. Three of these were taking 300 mg. of rutin or more daily while the other 2 were taking 180 mg. daily. It is significant that at the time of the hemorrhage 2 of these patients had a normal capillary fragility. Case 15137 was a 33 year old female with diabetes of 15 years duration who had typical diabetic retinitis. She had been taking rutin orally for 13 months and her original capillary fragility test showed a petechial index of 50 by the Göthlin technique. She took 180 mg. of rutin daily from June 1948 to July 1949. The results of her capillary fragility tests are shown in Fig. 1. It will be noted that the capillary fragility was reduced from a high of 250 petechiae in December 1948 to a low of 20 petechiae on April 30, 1949. On June 19, 1949, while her capillary fragility was still relatively low she had a massive vitreous hemorrhage in the left eye. The capillary fragility test done 2 days later showed far too many petechiae to count in the 6 cm. circle. During the next month following the hemorrhage the patient took 25 mg. of rutin subcutaneously in addition to the 180 mg. orally. At the end of the month the capillary fragility had returned to normal with a petechial count of 10 and there was subjective improvement in vision. This case illustrates that rutin therapy may not prevent retinal hemorrhages even though the capillary fragility returns to a relatively normal limit. However, it must be emphasized that in this case in addition to the diabetic retinitis the patient had massive albuminuria, peripheral edema, hypertension and hypoproteinemia. Case 4924 was a 49 year old female who had had diabetes for 24 years. In 1946 an ophthalmologist reported only a few small punctate hemorrhages in each retina. She was started on rutin therapy and during 1948 and 1949 she received 300 mg. of rutin daily. Her capillary fragility was never affected by the rutin therapy, remaining at a high level between 200 and 400 petechiae. In March 1949, 3 years after the ophthalmologist had described early diabetic retinitis, he stated that the patient showed marked retinitis proliferans in spite of the fact that she had been on rutin therapy. In contrast to the above may be cited the experience of Case 4672, a 29 year old female with onset of diabetes at the age of 4 years. In 1947 an ophthalmologist described retinitis proliferans. She was started on rutin, 120 mg. daily at that time. The dose was gradually increased to 400 mg. per day. During 19 months of treatment there was no progress in the retinitis observed by the ophthalmologist. The capillary fragility fluctuated between a high of 136 to a low of 12 petechiae.

Discussion. Munroe, Lazarus and Bell[5] have pointed out that there are a number of physiological factors affecting the results of the capillary strength determination. Capillary weakness was found in 10.7% of 103 male students and 21% of 19 healthy old men. Schraeder[9], using the Rumpel Leede test, found capillary weakness during menstruation. Roberts, Blair and Bailey[7] showed that there was a well marked tendency for capillary strength to follow a seasonal pattern roughly corresponding to the Vitamin C supply. There have been many reports correlating Vitamin C status and capillary strength. Turpeinen[10], using the Göthlin test, found that when 9 healthy children who had had high petechial counts were retested after 50 days during which no treatment was given a spontaneous decline had occurred

in the counts of 7 subjects. Bell, Lazarus and Munroe had similar results in 15 healthy children. Another factor which may influence the capillary fragility test is the length of time which has elapsed since positive pressure was last applied to the arm used. If the weak capillaries in the forearm are ruptured by positive pressure a period of time must elapse for recovery before repeating the test, else a false low petechial count may result. It is recommended that a minimum of 3 weeks be allowed to elapse before repeating the test on the same arm. Furthermore, it should be pointed out that the results may differ in the 2 arms when tested simultaneously. Other observers have stated that age, weather and the time of day may influence the results.

Rutin will strengthen capillaries in a minority of diabetic patients with retinitis, 25% in this group. However, as illustrated by the 5 patients who had severe hemorrhages following rutin therapy, 2 of whom had normal capillary fragility tests prior to the hemorrhage, rutin does not necessarily protect the patient against hemorrhage even when his capillary fragility has returned to normal with rutin therapy. In the 32 cases of retinitis treated with rutin in this series no case showed improvement in the retinopathy. A number of patients, however, expressed subjective improvement in vision. Again it must be pointed out, as emphasized by Hollenhorst and Wagener[4], that hemorrhagic retinal lesions of all types are subject to frequent remission. Diabetic retinopathy is a slow process in a majority of patients and it is thus difficult to note any change from month to month.

The exact petechial counts have not been presented in this group of patients with diabetic retinitis because there seems to be no relationship between the severity of the diabetes or the retinopathy and the height of the count. For example, Case 9077, a 29 year old woman with diabetes of 19 years duration, had severe retinitis proliferans despite the fact that the capillary fragility indexes were relatively low, 6 in June 1948 and 56 in December 1948. On the other hand, Case 11944 with no retinitis had a petechial index greater than 400 which persisted for 10 months in spite of 300 mg. of rutin daily. The latter case was given rutin subcutaneously, 25 mg. daily for one month in addition to the oral dose. The capillary fragility remained at the same level. Certainly factors are at work other than the capillary weakness in retinal hemorrhage. As yet it is by no means certain that fragility of skin capillaries is accompanied by a similar fault in the retinal vessels. The fact that in Case 15137 the petechial index became extremely high immediately following a vitreous hemorrhage, whereas prior to the hemorrhage it was close to normal, suggests that there may be a direct relationship.

Poor diabetic control in the young patient can precipitate early hemorrhages as illustrated by Case 34989, a 29 year old male diabetic of 10 years duration who had grossly neglected his diabetes and had had repeated attacks of acidosis and frequently had noted polyuria, polydipsia, fatigue and weight loss. When first seen after only 10 years of diabetes at the age of 29 there were punctate hemorrhages in the retinae. Just as poor diabetic control can precipitate retinitis early, so good control may put it off or prevent it. White[12] studied 192 patients who had had the disease for 20 or more years with onset at 15.0 years of age. Using diabetic coma as a criterion of poor control she observed that in 28 cases who had no evidence of retinitis, only 15% had ever been in coma. On the other hand, in 114

patients who had moderate retinitis, 40% had been in coma and in 50 cases who had severe, incapacitating, degenerative changes, 75% had one or more attacks of coma.

The question must still be answered, "Should rutin be used in the prophylaxis and treatment of diabetic retinitis?" From our studies there seems to be little objective evidence of its value, once retinitis has occurred since no improvement in the retinopathy took place. In our studies of capillary fragility there was no consistent trend noted while on treatment with rutin. There seems to be little difference in the results of those treated for 18 months or longer and those whose treatment was for shorter periods. Even with doses of over 300 mg. of rutin daily, only in 3 out of 10 patients so treated did the capillary fragility decrease. A few patients have been treated with rutin administered subcutaneously over short periods of time in dosage of 25 mg. daily. The number of patients studied is too small and the time of treatment too short to come to any conclusion about the subcutaneous administration of rutin.

Summary. 1. Two hundred and twenty diabetic patients were examined for evidence of diabetic retinitis and tested for capillary fragility, using a positive pressure method standardized on a group of 50 individuals without diabetes, hypertension, blood dyscrasia or nutritional deficiency.

2. Eighty patients had diabetic retinitis. Of these 68 (85%) had increased capillary fragility and in these the average duration of diabetes was 17.2 years. Twenty-five % of the 80 cases with retinitis were patients with onset of diabetes in childhood. Of the 80 cases of diabetic retinitis 49 (61.2%) had hypertension.

3. Sixty-eight cases had no retinitis but increased capillary fragility. The average duration of diabetes in this group was 11.4 years. Thirty cases (44.1%) had hypertension.

4. Seventy-two cases had normal retinae and normal fragility tests. The average duration in this group was 10.5 years. Twenty-four cases (33%) had hypertension.

5. Long duration of diabetes and hypertension are factors which predispose to diabetic retinitis. Poor control of diabetes may lead to early retinitis.

6. Thirty-eight patients with abnormal capillary fragility, 32 with retinitis and 6 without, were treated with rutin orally for a period varying from 6 weeks to 33 months. Even in daily doses of over 300 mg. and for long periods of time, for 18 months to 30 months rutin seemed to have little effect in improving either capillary fragility or diabetic retinopathy. Retinitis proliferans in a long-duration case may progress while on rutin therapy. Good control of diabetes over the years seems to be the best prophylaxis against retinitis. It is suggested that routine retinoscopy and capillary fragility tests be done at regular intervals on all diabetics. If treatment is begun early rutin may be of some value.

7. The place of rutin in the treatment of diabetic retinitis is still not conclusively established and a proper evaluation must await further study.

I am indebted to Dr. Eugene C. Eppinger of the Peter Bent Brigham Hospital for the privilege of doing capillary fragility tests on the patients of the Medical Service of the hospital

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THE REVERSIBILITY OF GLYCOGEN NEPHROSIS IN ALLOXAN-TREATED DIABETIC RATS*

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Within the recent past, the incidence of glycogen nephrosis found in post mortem examinations of diabetic patients has dropped remarkably. In the pre-insulin days Warren[6] states that it was found almost invariably in every diabetic patient. In the years 1932 to 1942, inclusive, the incidence dropped to approximately 42% of the diabetic patients autopsied at the Mallory Institute of Pathology of the Boston City Hospital[5]. Since that time at this same laboratory the frequency has fallen to below 10%[4]. There is little doubt but that this decreased incidence is the result of the better control with insulin of diabetes and its associated glycosuria. Warren and Root[7] have postulated, from clinical evidence, that the renal tubular lesion is merely a reflection of glycosuria, not a specific metabolic lesion of diabetes mellitus[7]. Experimental corroboration of this relationship has recently been offered by Curtis, Robbins and Glickman[1]. In the alloxan diabetic rat it was shown that glycogen nephrosis was causally related to the height of the hyperglycemia and its concomitant glycosuria. It was further demonstrated that only the terminal levels of hyperglycemia just prior to the sacrifice of the animal were significant in determining the appearance of glycogen nephrosis. If the animals were sacrificed with blood sugar levels above 350 mg. per 100 cc., glycogen nephrosis was invariably present, while animals with terminal blood sugar values below this level failed to show the lesion. The duration of the diabetes, the initial blood sugar levels, as well as the course of the diabetes, were of no consequence in the production of this tubular change. These results, therefore, strongly suggest that the development of glycogen nephrosis in rats is simply the reflection of the excretion of large amounts of glucose.

In several instances rats having high initial blood sugar levels, above 350 mg. per 100 cc., showed with the passage of time progressive decrease in the severity of the diabetes. Sacrifice of these animals at a time when the terminal sugar levels were below 350 mg. per 100 cc., failed to demonstrate glycogen nephrosis. It seemed reasonable to infer that had these animals been killed at an earlier date, when the hyperglycemia was above 350 mg. per 100 cc., glycogen deposits would have been present in the tubular epithelium. It was hypothesized, therefore, that glycogen nephrosis was a reversible lesion and fluctuated in relation to the height of the blood sugar level. The present communication offers further evidence in the alloxan diabetic rat of this lability of glycogen nephrosis to the point of its complete reversibility.

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Materials and Methods. The technique employed consisted essentially of removing first one kidney, then the other some time later, from rats rendered diabetic with alloxan. After a preliminary period of approximately 3 to 4 weeks of diabetes, unilateral nephrectomy was performed, followed in 3 to 4 weeks by removal of the remaining kidney. These kidneys were then studied histologically, correlating the severity of the glycogen nephrosis with the height of the hyperglycemia at the time of biopsy. This method permitted the evaluation in any individual rat of the effect of changing blood sugar levels on the severity of the glycogen deposit in the renal tubular epithelium.

Adult albino rats weighing approximately 200 to 250 gm. each were rendered diabetic by the administration of a single dose of alloxan monohydrate subcutaneously, according to the standard technique summarized by Lukens[3]. The dosage employed varied between 150 and 200 mg. of alloxan per kg. of body weight of rat. All animals, unless otherwise specified, were maintained on a diet of rat pellets and water *ad libitum*. Individual rats, preferably those having blood sugar levels above 350 mg. per 100 cc., were submitted to unilateral nephrectomy after approximately 3 to 4 weeks of diabetes. The animals were then maintained for an additional 3 to 4 weeks, some on a limited amount of food, supplemented occasionally by insulin in an effort to produce a remission in the diabetes or bring about a lowering of the blood sugar level. A certain number of animals, some treated with insulin, others untreated, responded with a fall in blood sugar levels, some to below 350 mg. per 100 cc. Thus it was possible to examine one kidney of a diabetic rat while the blood sugar level was high, above the critical level, and the other kidney at some time later when the animal's blood sugar level had fallen to below 350 mg. per 100 cc. It was thus possible to determine whether decrease or disappearance of the glycogen nephrosis had occurred.

The blood sugars of individual rats were determined approximately every 10 days, using the Folin-Malmros technique[2]. Since it was found that unilateral nephrectomy did not alter the severity of the course of the diabetes, and since it is known that glycogen deposition is invariably bilateral, nephrectomy rather than biopsy was employed, being technically simpler. Blood sugar values were always determined simultaneously with the removal of each kidney. The tissues were fixed in absolute alcohol for Best's carmine glycogen stain and in Zenker's fixation for phloxine-methylene blue stain. The glycogen deposit was then evaluated and classified according to the severity of deposition of glycogen, 0 to 4 +. All histologic evaluations were done without knowledge of the blood sugars.

Results. A total of 343 adult albino rats were used. Of the total number of animals injected, 148 survived the immediate post-injection period. Many of these surviving animals died or were otherwise unsuitable for our purposes and 41 rats were finally selected for biopsy study.

Of the 41 rats selected for tissue study 10 rats died after the first nephrectomy, the remaining 31 being used to study serially both kidneys as previously described.

Initial blood sugar levels up to 1060 mg. per 100 cc. were obtained. The 41 rats showed the following distribution of initial blood sugar levels:

Number of Rats	Initial Blood Sugar Tests Glucose mg. per 100 cc.
4	150 to 249
3	250 to 349
8	350 to 449
8	450 to 549
4	550 to 649
4	650 to 749
10	above 750

After a 3 to 4 week period, just prior to the initial nephrectomy, the blood sugar levels had shifted, some rising, most falling, with the following distribution:

Number of Rats	Pre-nephrectomy Blood Sugar Levels Glucose mg. per 100 cc.
13	150 to 249
5	250 to 349
6	350 to 449
4	450 to 549
4	550 to 649
4	650 to 749
5	above 750

The initial unilateral nephrectomy apparently altered the diabetic course of many of the rats; some, however, showed no apparent reaction to the removal of one kidney. This alteration in the trend of the diabetes took the form of increasing severity of hyperglycemia in some rats, with a sudden fall in blood glucose levels in others. The direction of change could not be correlated with any obvious factors and since these changes seemed to represent a random pattern, they tended to cancel out each other as far as the present study is concerned.

In individual rats the amount of glycogen nephrosis found at nephrectomy definitely appeared to be related to the level of the blood sugar as was shown in an earlier study[1]. The blood sugar levels of some individual animals are charted below, with the figures in the circles indicating at the time of the nephrectomy the severity of glycogen nephrosis (Chart 1). It can be seen that in most animals the glycogen deposit varied proportionally to the blood sugar levels. As the sugar level fell, so did the quantity of tubular deposition of glycogen. Perhaps the most clear-cut evidence of this change was found in the few animals with falling sugar levels which, having glycogen at the time of the first nephrectomy, were found at the time of the second nephrectomy to have no glycogen. Other rats less striking than these showed unequivocal diminution in the amount of glycogen as the blood glucose levels fell. The converse was equally true. With increasing severity of diabetes there was a greater deposition of glycogen at the time of the second nephrectomy.

In those rats in which glycogen nephrosis had been present and then had disappeared, it was of particular interest to study the second kidney to determine whether residual damage to the nephrotic tubular cells might be apparent. Routine cellular stains showed, at a time when all the glycogen had disappeared, no residual demonstrable anatomic change in the renal epithelium (Figs. 1 and 2). As far as could be determined from routine stains the tubular epithelium had reverted to normal. Since no early "post-alloxan"

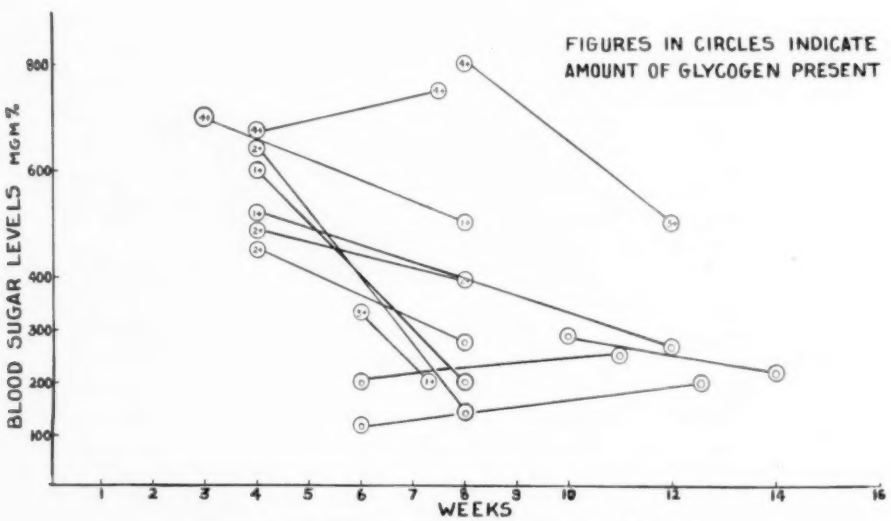

CHART 1. Blood Sugar Levels of Individual Rats.

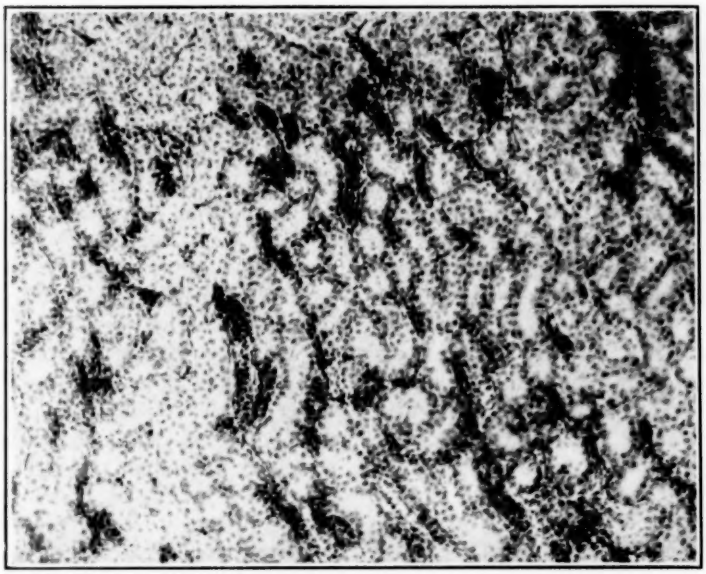

FIG. 1. Nephrectomized kidney from diabetic rat with blood sugar above 350 mg. per 100 cc. Deeply stained tubules contain glycogen. Best's carmine stain (x 200).

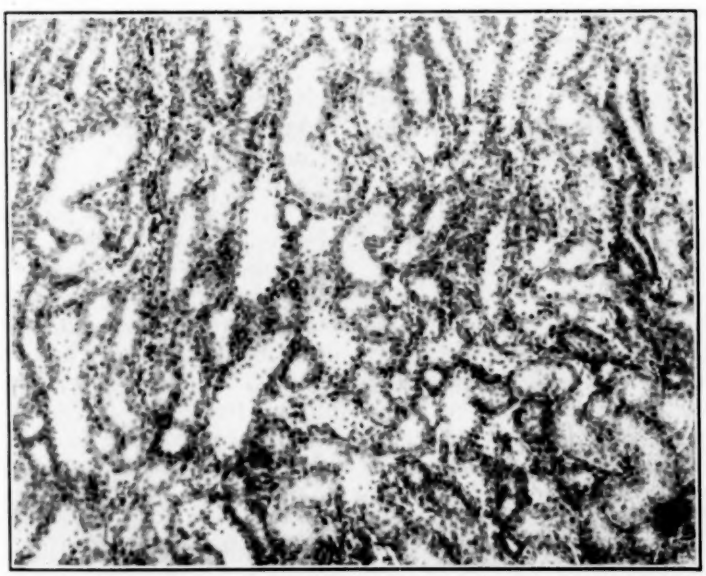

FIG. 2. Remaining kidney from same rat after blood sugar level had fallen to below 350 mg. per 100 cc. Note absence of glycogen and apparent normality of renal tubular epithelium Best's carmine stain (x 200).

rats were studied, necrotic or destructive tubular epithelial lesions were completely absent in these kidneys. No changes in glomeruli or vessels were apparent. The kidneys appeared only slightly larger grossly, but this increase in size could not be correlated with any specific histologic lesion.

Discussion. The above results would appear to confirm the impression gained from earlier experiments that glycogen nephrosis is a physiologic change occurring in renal tubular epithelium in response to a significant glycosuria. It is directly proportional in amount to the height of the hyperglycemia and severity of glycosuria. When the levels of hyperglycemia, initially however high, fall below the value of 350 mg. per 100 cc., shown previously to be the critical level, the glycogen nephrosis previously present in the kidneys will disappear. After disappearance of the glycogen the perfectly normal histologic appearance of the tubular epithelium attests to the probable physiologic nature of this glycogen deposit. While it is theoretically possible that the previously vacuolated cells had been destroyed and had been replaced by regenerated epithelium at the time of the second renal biopsy, the total absence of any evidence of regeneration over the varying time intervals studied militate against this possibility. Just as glycogen nephrosis may decrease in severity or disappear, with rising sugar levels, it obviously may become more severe. Few conclusions could be drawn referable to the speed with which glycogen might be withdrawn from the kidney. While it is known that glycogen may appear within the first few days after the administration of alloxan, the impression was gained by these studies that disappearance occurs somewhat more slowly. In many of the rats glycogen nephrosis persisted, although at lower levels, for several weeks after the blood sugar levels had fallen below 350 mg. per 100 cc. Since differences in the amount of glycogen must be fairly marked before they are definite visually, the above observations must of necessity be interpreted within wide limits.

Quite apart from these changes in glycogen deposit within the renal tubular epithelium, the effect of unilateral nephrectomy on the course of the diabetes was of some interest. It appeared possible that sudden sharp reduction in the excretory capacity of the rat might reflect itself in diminished glucose excretion and elevated blood sugar levels. While this phenomenon did occur in some animals, it was matched by exactly the opposite change in others, the diabetes becoming significantly less severe after nephrectomy. This remission in severity was not simply post-operative loss of appetite of the animal, since the downward trend still persisted for long periods after the surgery. It is entirely possible that these alterations in the course of the diabetes were essentially coincidental with the nephrectomy, simply being accentuated by the marked metabolic disturbances incidental to the surgery and anesthesia.

Summary. A study on alloxan diabetic rats of the effect of changes in the blood sugar levels on the severity of glycogen deposit in the renal tubular epithelium is reported. Forty-one rats were submitted to unilateral nephrectomy after a period of 3 to 4 weeks of diabetes. After an additional 3 to 4 weeks the second kidney was removed from the 31 surviving rats. Thus it was possible to determine the effect of changing hyperglycemic levels on the renal epithelium. It was obvious that the severity of glycogen nephrosis in any individual animal did not remain constant, but fluctuated proportionally to and in response to the blood sugar level.

In several instances well-established glycogen nephrosis disappeared as the hyperglycemia fell to below the critical level of 350 mg. per 100 cc. The results confirmed earlier impressions that glycogen nephrosis is due to a physiologic deposit of glycogen in renal tubular epithelium following and reflecting the changing blood sugar levels. Complete reversibility with total disappearance of glycogen nephrosis may occur. The tubular epithelium in these instances apparently completely reverts to normal.

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THE DIAGNOSIS AND TREATMENT OF TUBERCULOUS MENINGITIS IN CHILDREN*

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Recent advances in chemotherapy have stimulated renewed interest in the clinical picture of tuberculous meningitis. When meningitis was still an almost universally fatal form of tuberculosis, there was little incentive to make an early diagnosis. With the possibility of cure it became important to recognize the first symptoms of tuberculous meningitis. Moreover, it is essential in the evaluation of chemotherapeutic agents that serous tuberculous meningitis be distinguished from caseous meningitis, since spontaneous recovery from serous meningitis is not uncommon.

Diagnostic Signs and Symptoms. The character and duration of the prodromal symptoms of tuberculous meningitis were studied in a group of 167 unselected cases from the Children's Medical Service of Bellevue Hospital[8]. It was found that the early symptoms of tuberculous meningitis are those often seen in children with minor illnesses: fever or sudden rise in fever, vomiting, drowsiness or apathy. Irritability also may be noted at the onset of meningitis. In spite of the important role assigned to constipation as an early symptom in many text books, it has not been common in our series, occurring in less than 10% of cases. In the older child, headache may be a prominent and helpful early diagnostic symptom. It occurred in 60% of our patients who were at least 4 years old, but was not noted under the age of 3. A generalized convulsion dated the onset of tuberculous meningitis in about 20% of patients under 2 years old, but was an uncommon symptom after this age and was not noted in children over 5 years old.

An analysis of 75 cases of tuberculous meningitis not known to be tuberculous before admission to the hospital, revealed that 47 were diagnosed within the first 24 hours. In 10 additional cases the initial diagnosis was brain tumor or brain injury, or poliomyeloencephalitis; one infant was at first thought to be mentally deficient because of marked apathy. In almost all cases not diagnosed on admission, meningitis was first suggested by positive tuberculin reactions, subsequent chest Roentgen-rays and by the results of spinal fluid examinations.

The Clinical Picture of the Untreated Case. In most cases the onset of tuberculous meningitis was gradual, the neurological examination remaining normal during the first stage of general symptoms. During the second stage of increasing stupor the neuro-

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logical signs were at first often transient; hyperactive deep reflexes, diminished abdominal reflexes, positive Kernig and Brudzinski signs and ankle and patellar clonus were frequently noted. Evidence of involvement of the cranial nerves, most often ptosis, strabismus, nystagmus or facial paralysis occasionally appeared during this second stage. Peripheral paralysis and clonic spasms of one or more extremities were sometimes noted as early neurological signs. Fixed or unequal pupils, and irregular respirations of the Biot type were occasionally seen in the second stage, but more commonly in the final or comatose stage of the disease. Some degree of nuchal inflexibility was usually seen early, but a rigidity was often a late sign. The final stage of the disease was usually one of steadily increasing stupor with periods of return to consciousness in rare instances. In the group of cases studied, the duration of tuberculous meningitis from the first symptoms to death varied from 1 to 63 days. Often the 3 stages of the disease were of about equal length. Occasionally the stage of general symptoms was prolonged. In cases of short duration the neurological signs often appeared at the same time as the general symptoms.

With the advent of chemotherapy it became important to diagnose tuberculous meningitis as soon as possible. Since the early symptoms of meningitis are also often seen in children with minor illnesses, it is obvious that most really early diagnoses will be made in children previously known to be tuberculous. A group of 92 children with primary tuberculosis who developed tuberculous meningitis while under observation gave us the opportunity to study the time relationship between the onset of tuberculosis and the first symptoms of meningitis. Of these, 77% died of meningitis less than a year after the first diagnosis of tuberculosis; over 42% of the cases of meningitis occurred within 3 months after primary tuberculosis was discovered.

Therefore, in a child with a manifest primary tuberculosis the physician should look with suspicion on general symptoms whose cause is not obvious, or on symptoms with an apparent good explanation which do not yield to appropriate therapy. Daily fever or sudden rise in fever with no adequate cause should be a danger signal. A convulsion in a tuberculous child, especially in an infant, should always be an indication for an immediate lumbar puncture. Unexplained fever, drowsiness, and vomiting should suggest the possibility of meningitis in any tuberculous child, regardless of the duration of the disease, when there has been a recent history of a factor which might predispose to tuberculous meningitis: measles or pertussis, a severe fall, a general reaction to a tuberculin test.

Prompt recognition of tuberculous meningitis will be more difficult when the child is not known to be tuberculous. Early diagnosis will be accomplished in an increasing number of cases, however, if routine Mantoux tests are done in children with fever or general symptoms of unknown origin. In our series of cases, anergy to tuberculin was found to be relatively uncommon even in well-developed cases of meningitis, since positive reactions were obtained in at least 85% of the children. A chest Roentgen-ray may also be of value in diagnosis, since over 90% of our cases of tuberculous meningitis who were not known to be tuberculous before admission to the hospital gave positive evidence of tuberculosis on chest Roentgen-ray; manifest primary tuberculosis was present in over 75%. The child who has a convulsion as an initial symptom will

only be diagnosed promptly if a lumbar puncture is done. The search for a cause for the convulsion should include a Mantoux test.

The case of short duration, the fulminating case and the case associated with an incidental infection of obvious origin will present the greatest obstacles to early diagnosis.

The object of chemotherapy early in the course of the disease is not only to effect a higher percentage of survivals but also to prevent irreversible cerebral changes. There is evidence that the chances of developing hydrocephalus of more than slight degree increase with the duration of tuberculous meningitis. Therefore, a patient with a short history would have a better chance of complete restitution to normal.

The spinal fluid of tuberculous meningitis fortunately is often characteristic. A clear fluid with cells ranging in number from 10 to 350 per cmm. was found in 86% of our cases; rarely, especially in the fulminating case, the cells may be increased even over 1000 per cmm. In 87% of our cases lymphocytes predominated; the finding of a high proportion of polymorphonuclear leukocytes is usually associated with rapidly progressive cases. The fluid on standing usually develops a pellicle in which tubercle bacilli can frequently be demonstrated on direct examination. In a few cases, even when the diagnosis is substantiated by autopsy, tubercle bacilli cannot be demonstrated even by culture and guinea pig inoculation. The protein content of the spinal fluid tends to be high and to rise as the disease progresses. In the series of cases studied before the advent of chemotherapy the initial spinal tap showed a fluid with a protein content above average in over 99% of our cases; in over half the cases it exceeded 50 mg. per 100 cc. The sugar content of the spinal fluid even on the initial tap tends to be low. It was below 38 mg. per 100 cc. in 96% of our cases. Excluding the finding of tubercle bacilli, the low sugar content is the single most valuable diagnostic finding in the spinal fluid. Next in importance is a progressive decline in the sugar content, even if it remains close to normal. There are exceptions, of course, to this general rule. Four children in our original series of cases had a spinal sugar content of over 55 mg. within a week of death. In general, however, a clear fluid with a moderate pleocytosis, mainly lymphocytes, with a sugar content which tends to be low and a protein content above normal should rouse suspicion of tuberculous meningitis, especially if a pellicle develops on standing.

Diagnosis of Tuberculous Meningitis. With chemotherapy available as a potent weapon, every effort must be made to diagnose tuberculous meningitis early. Children with primary tuberculosis should have spinal fluid examinations whenever the suspicion of meningitis is aroused by general symptoms. Even when the primary tuberculosis is known to be of at least a year's duration, the possibility of meningitis must not be overlooked. Its occurrence becomes more unlikely as healing of the primary tuberculosis progresses. Tuberculous meningitis must be considered in differential diagnosis as soon as any child presents evidence of meningeal irritation, even if nothing in the history or examination suggests tuberculosis. Tuberculin test and chest Roentgen-ray often furnish the first evidence pointing to the tuberculous origin of the meningitis in cases at first considered to be of suppurative or viral origin.

Actually, once the spinal fluid has been examined, the number of conditions which can be confused with

tuberculous meningitis is small. A clear fluid with a moderate pleocytosis is seen in viral infections, such as lymphocytic choriomeningitis. The chemical changes are, however, not marked and the sugar rarely sharply reduced. A fluid typical of tuberculous meningitis may occasionally be seen in chronic influenzal meningitis especially in the presence of a walled-off abscess. However, influenza organisms should be demonstrated on direct examination or certainly by culture within 24 hours. It is unfortunately true that children with tuberculous meningitis are occasionally treated as cases of influenzal meningitis because a few possible organisms were seen. In such cases, Mantoux tests and chest Roentgen-rays have been delayed until there is evident failure of response to therapy, and even if the tuberculous meningitis can be arrested, the chance for a complete restitution to normal may have been lost. If a second examination of the spinal fluid within 24 hours shows no definite organisms, in the presence of a rising protein and falling sugar content, a presumptive diagnosis of tuberculous meningitis should be made and treatment started.

TABLE 1. RESULTS OF TREATMENT WITH STREPTOMYCIN AND PROMIZOLE

(Data as of July, 1949.)

Case	*Age at Onset*	*Roentgen-Ray Evidences of Tuberculosis*	*Results*
1. E. S.	9 mos.	Primary	Hydrocephalus on admission. Died 66th day of treatment.
2. H. R.	11 yrs.	Miliary; Spondylitis	Spinal fusion after recovery. Well 27 months after meningitis.
3. J. Y.	4 yrs.	Miliary	Died during relapse 11 months after onset of miliary.
4. L. W.	3 yrs.	Primary	Well 26 months after meningitis.
5. E. D.	2 yrs.	Primary	Well 25 months after meningitis.
6. S. E.	6 yrs.	Primary	Well 24 months after meningitis.
7. O. V.	23 mos.	Primary	Well 22 months after meningitis.
8. B. P.	3 yrs.	Calcified Primary	1st relapse 43 days, 2nd relapse 44 days after completing previous courses of treatment. Spastic paralysis right; deaf. Doing well 6 months after 2nd relapse. 20 month follow-up.
9. A. M.	8 mos.	Miliary	Spastic paralysis right. Otherwise well 18 months after meningitis.
10. M. M.	5 yrs.	Calcified Primary	Relapsed 45 days after completing treatment. Atrophy left leg with foot drop; 18 months since onset.
11. R. Co.	13 mos.	Miliary	Good condition 13 months after onset.
12. M. P.	6 yrs.	Calcified Primary	Good condition 13 months after onset.
13. G. V.	10 mos.	Primary	Died 10th day of treatment.
14. M. G.	11 mos.	Primary	Died 18th day of treatment.
15. V. O.	15 mos.	Primary	Good condition 12 months after onset.
16. M. K.	5 yrs.	Calcified Primary	Good condition 11 months after onset.
17. C. M.	13 mos.	Primary	Died 39th day of treatment—exfoliative dermatitis
18. W. M.	2 yrs.	Clacified Primary	Good condition 9 months after onset.
19. M. L.	4 yrs.	Calcified Primary	Under treatment 4 months.
20. F. F.	13 mos.	Primary	Under treatment 3 months.
21. F. J.	10 mos.	Miliary	Under treatment 3 months.

The diagnosis of tuberculous meningitis may be especially difficult in children with miliary tuberculosis who are already receiving streptomycin by the intramuscular route. Such children should be carefully watched for early general symptoms of meningitis, such as somnolence or increased irritability. In 2 of our cases of miliary tuberculosis who developed meningitis while under streptomycin therapy the sugar content of the cerebrospinal fluid remained normal even after tubercle bacilli could be demonstrated by culture. An elevated protein content of the spinal fluid in a child with miliary tuberculosis should be checked in 24 hours and, if further increased, should be an indication for treatment even in the absence of a diminished sugar content. In such cases the streptomycin levels of the spinal fluid may be of great value as confirmatory evidence of local inflammatory changes in the meninges. In the absence of meningitis the levels of streptomycin in the spinal fluid are usually not over 3 micrograms per 100 cc. In 2 patients with miliary tuberculosis streptomycin levels of 5 to 40 micrograms were obtained in the spinal fluids before other evidence of tuberculous meningitis was obtained. This masking of the diagnosis of meningitis in miliary tuberculosis because of normal sugar values has stimulated a search for other tests by which early diagnosis of meningitis can be established. The Levinson test and colloidal gold curves may be of value. In children where meningitis was not present, the Levinson test was invariably negative and the colloidal gold curve normal.

Serous Tuberculous Meningitis. In contrast to the child with caseous tuberculous meningitis who in our series invariably died of his disease, tuberculous children may exhibit physical signs and symptoms very suggestive of meningitis and go on to complete recovery. This clinical picture which we have called serous tuberculous meningitis[9] is not uncommonly seen on a ward for children with active tuberculosis; it should be considered in the differential diagnosis of tuberculous meningitis preparatory to chemotherapy.

Serous tuberculous meningitis is probably due to a perifocal reaction around seedings in the early primary or post-primary stage of tuberculosis or to later collateral inflammation around older caseous foci in the cortex or meninges. Such lesions have been demonstrated pathologically in children who died soon after an attack of serous meningitis; in these cases no evidence of tuberculous meningitis was found.

In the first stages of caseous tuberculous meningitis the differentiation from serous meningitis cannot be made by the clinical picture. Headache, irritability, fever, drowsiness and vomiting are as commonly associated with the onset of serous meningitis as with caseous meningitis. Miliary tuberculosis is frequently associated with either, and its presence therefore does not help in differential diagnosis. The early neurological evidences of caseous meningitis, such as stiff neck, positive Kernig and Brudzinski signs, may also be seen in serous meningitis. Very marked early general symptoms followed by scanty neurological signs should suggest the possibility of serous tuberculous meningitis. Ankle clonus associated only with some degree of stiff neck is the most common neurological sign associated with serous meningitis. Another finding which favors the diagnosis of serous meningitis is Roentgen-ray evidence of recent local extension of the pulmonary tuberculosis. On the other hand, a convulsion at onset would strongly suggest a tuberculous meningitis, since we have no

record of a generalized convulsion in a case of serous meningitis, although several children had marked tremor or clonic spasms of the extremities. Involvement of the cranial nerves, except facial paralysis which may be due to tuberculous otitis media, is also not recorded in our cases of serous meningitis. No case of serous meningitis has been really comatose although some were very drowsy. On clinical examination alone it is impossible to distinguish a caseous tuberculous meningitis from a serous tuberculous meningitis. The differential diagnosis may even be difficult in the second stage, but in the third stage of caseous tuberculous meningitis the diagnosis should be obvious on physical examination. However, one cannot afford to delay chemotherapy until the diagnosis is firmly established by the clinical picture.

The differential diagnosis can be made earlier and more easily by the results of examination of the spinal fluid. While an increase in spinal fluid pressure and in number of cells may be present in either form of meningitis, we have found no changes in chemical constituents in serous meningitis; the sugar, protein and chloride content of the spinal fluid remained within normal range. No pellicle developed in the spinal fluid of a case of serous tuberculous meningitis and no tubercle bacilli were found on direct examination or culture. The finding of a few tubercle bacilli is not incompatible with a diagnosis of serous tuberculous meningitis; in such cases the sugar and protein content of the spinal fluid should be checked daily, since the finding of a few bacilli may be a warning of the possible transition from a serous to a caseous meningitis. The presence of tubercle bacilli in the spinal fluid has been reported by MacGregor and Green[12] in cases showing no evidence of tuberculous meningitis on postmortem examination. These authors conclude that "localized lesions in the central nervous system may be set up by hematogenous infection of a mild sporadic type, not meriting the name of miliary tuberculosis. There is evidence that on such occasions tubercle bacilli may be present, probably temporarily, in the cerebrospinal fluid, that occasionally clinical symptoms and signs may mark the occurrence of this initial infection and that such incidents are not necessarily followed by the development of fatal tuberculous meningitis."

Rich[20] describes 2 cases of meningitis due to caseous cortical foci which had shown transient signs of meningeal irritation some weeks before signs of diffuse meningitis developed. Because of the possibility of subsequent caseous meningitis every patient with serous tuberculous meningitis should be kept under close supervision for several months. Even if the symptoms subside rapidly at least one later examination of the spinal fluid should be made. If follow-up examination of the spinal fluid is done, chemical changes in the spinal fluid indicating a meningitis would be discovered promptly and treatment could be instituted at once. It is our opinion that serous tuberculous meningitis should not be treated by streptomycin, since in the great majority of cases there is spontaneous disappearance of symptoms. Every effort should be made to protect such children from factors which have been thought to precipitate meningitis. A child who has had serous tuberculous meningitis should not be excessively exposed to sunlight; he should be protected from unnecessary exposure to measles or pertussis; he should not be subjected to tuberculin testing and surgical operations should not be undertaken unless they are essential.

TREATMENT OF TUBERCULOUS MEN-

INGITIS. Once the diagnosis has been established, treatment should be vigorously pursued. The use of streptomycin is definitely indicated in tuberculous meningitis. The physician must, however, decide whether streptomycin should be administered by the intrathecal as well as by the intramuscular route and whether it should be used as the sole therapeutic agent or combined with another tuberculostatic drug. Hoyne[5] and Levinson[7] have protested the use of intrathecal streptomycin. There is no doubt that some cases of tuberculous meningitis can be cured with streptomycin given only by the intramuscular route. However, as the report of the British Medical Research Council clearly demonstrated[14], the number of cases cured by combined intramuscular and intrathecal therapy is greater than with intramuscular treatment alone. Therefore, since our goal should be the cure of as many cases as possible, the use of intrathecal therapy in addition to intramuscular seems clearly indicated.

On the Children's Medical Service of Bellevue Hospital, tuberculous meningitis has been treated since December, 1946, with streptomycin combined with a sulfone, promizole. There were many reasons for combining another drug with streptomycin. It was obvious from reports in the medical literature that streptomycin far surpassed any previous tuberculostatic agent. The prolonged use of this antibiotic, however, not infrequently causes the emergence of drug resistant tubercle bacilli. Streptomycin, moreover, has a selective toxicity for the 8th nerve and particularly the vestibular branch; ataxia appears with great regularity after administration of streptomycin for relatively short periods. It seemed possible that the use of 2 different types of bacteriostatic agents might delay or diminish the chances of developing drug resistance. Smith *et al.*[21] had shown in experimental animals that the effect of streptomycin was enhanced by the addition of a sulfone; the therapeutic result of the combined therapy was greater than the simple summation of the effect of the 2 drugs. The frequency of reported relapses of tuberculous meningitis after treatment with streptomycin convinced us of the need for the prolonged use of tuberculostatic agents. Since streptomycin is unsuitable for such use because of its toxicity and its tendency to cause drug fastness, it seemed desirable to combine it with another drug which could be used safely and effectively for years.

Our previous experience with promizole led us to select this sulfone to combine with streptomycin. We had begun to use promizole in 1944 by attempting treatment of 5 cases of tuberculous meningitis; all of them died with no deviation from the usual course and duration of the disease. We then decided to use the sulfone in miliary tuberculosis, since this was almost as universally fatal a form of tuberculosis as meningitis but was usually of longer duration, thus allowing more time for action of a therapeutic agent. Five of 7 cases of acute generalized miliary tuberculosis treated with promizole for more than a month showed complete recession of the miliary tubercles on Roentgen-ray in 6 to 12 months. A decision to continue therapy for a long period of time was based on experimental work published by Feldman, Hinshaw and Moses[4], showing the frequency of relapses in animals apparently cured by sulfones; Medlar and Sasano[15] demonstrated viable tubercle bacilli in the spleens of apparently cured animals. The need for prolonged therapy was further confirmed by our patients, some of whom continued to develop extra-pulmonary complications while the miliary mot-

tling was receding on Roentgen-ray. In order to maintain prolonged bacteriostatic action it was decided to continue treatment with promizole after the miliary tuberculosis was apparently arrested, and 3 years was arbitrarily decided on for the duration of therapy. The 5 cases of miliary tuberculosis are all leading normal lives at home 3 to 5 years after treatment was begun and are free from miliary tuberculosis. None of these cases has relapsed nor developed tuberculous meningitis. Details of these cases have been previously published[10,11,16]. Because of these results we were convinced that promizole had an inhibitory effect on hematogenous tuberculosis in children; previous study had demonstrated the frequent association of hematogenous tuberculosis with meningitis in children with manifest primary tuberculosis. Promizole has the disadvantage of acting slowly, and it is inadequate as a sole therapeutic agent in meningitis and in rapidly progressive cases of hematogenous tuberculosis. But it possesses the advantage of ease of administration, since it is given orally and has relatively slight toxic effects. By the simultaneous use of streptomycin and promizole it was hoped that the child with tuberculous meningitis would benefit from the rapid action of streptomycin; the bacteriostatic effect would be still further enhanced by gradually increasing doses of promizole; after apparent arrest of the disease had been secured, therapy could be continued with the sulfone which can apparently be given safely and effectively for years.

Dosage. During the treatment of our first cases using combined streptomycin and promizole there was some variation in dosage of streptomycin; the daily intramuscular dose varied from 0.5 to 2.0 gm. Except for these first cases, we have given 1 gm. of streptomycin daily to all patients regardless of the age or size of the child: in a single dose to well nourished older children; 0.5 gm. twice daily to infants or emaciated children. Streptomycin intramuscularly is continued for 180 days. In addition, 0.1 gm. is given daily by the intrathecal route until toxic symptoms occur or mechanical difficulties arise. If toxic symptoms recur, 0.05 gm. to 0.1 gm. is given every second or third day. The course consists of 40 intrathecal injections. If relapse occurs, the full course of streptomycin is repeated by both intramuscular and intrathecal routes.

Promizole is given orally at 6 hour intervals. An initial dose of 0.5 to 1.0 gm. daily is given. In the absence of evidence of toxicity, the dose is gradually increased until a blood level of 1.0 to 3.0 mg. per 100 cc. is obtained; this is the level with which therapeutic results were obtained in the children with miliary tuberculosis. Absorption curves in children taking promizole show that the peak is reached 2 to 4 hours after oral administration of the drug. Blood for determination of level should be taken during this period. It is our practice to estimate the blood level on samples of blood taken 3 hours after promizole has been given. There is no apparent relation between the level obtained and the dosage or weight of the child. Adequate levels have been obtained with dosage varying from 0.375 gm. to 8 gm. daily. It is planned to continue treatment with promizole for 3 years until the results of treatment can be assessed in a group of at least 25 cases of meningitis.

Toxic Effects. The toxic effects of promizole when given alone have been discussed in previous publications. In the cases where it has been given in combination with streptomycin relatively few toxic effects have been seen. It is possible that the evidence of les-

sened toxicity is due to the small initial doses used and to the gradual increase in the amount of drug given. All children receiving promizole continue to show, at times, a cherry red or pink urine; the significance of this finding is not known. Most of the children have been slightly but not constantly cyanotic. The goitrogenic effect of promizole has been evident in most cases after several months' administration of the drug; the cholesterol content of the blood sometimes becomes elevated and the thyroid gland palpable. In only a few cases has definite enlargement of the thyroid gland been noted; the administration of small amounts of desiccated thyroid apparently counteracts the goitrogenic action of promizole. One girl 6 years old (Case 6) has shown evidence of the stimulating effect of promizole on secondary sex characteristics; after 8 months of promizole therapy she showed definite evidence of mammary gland development.

Toxic reactions of streptomycin have been similar to those reported by all investigators. Vomiting was frequent, especially during the first weeks of administration of the drug; however, in only 1 case was this symptom so severe that therapy had to be temporarily discontinued. Four children had generalized papular or urticarial eruptions, in 2 cases associated with or followed by eosinophilia. In one patient the rash developed into exfoliative dermatitis (Case 17). Only 1 child showed an elevated blood nonprotein nitrogen, associated with cylindruria, and this finding was of brief duration. Four patients became deaf during the course of treatment but in only 2 cases has the deafness persisted after treatment with streptomycin was discontinued. There is, of course, no way of knowing whether the deafness was due to meningitis or to the treatment.

The most constant toxic result of streptomycin therapy was the effect on the vestibular branch of the 8th nerve. Every patient gave some evidence of ataxia after 3 to 4 weeks of treatment. Clinically, every child who recovered made an apparently satisfactory adjustment; no child has had permanent symptoms of ataxia. Evidence obtained by a simple caloric test (the Kobrak test), however, proved that response to stimulation was invariably lost and sometimes as early as the 2nd week of therapy. Recently 5 of our early cases were retested, all more than a year after streptomycin had been discontinued. Four had regained normal response to caloric stimulation as judged by the Kobrak test.

Dihydrostreptomycin has been used in our last 3 cases of meningitis, and loss of response of the vestibular branch of the 8th nerve to caloric stimulation has occurred later than when streptomycin was used. We have, as yet, not completed therapy with dihydrostreptomycin in a case of meningitis, but in other forms of tuberculosis treated with dihydrostreptomycin the vestibular response returned within a few weeks after therapy was discontinued.

Following intrathecal administration of streptomycin, increased vertigo and ataxia, transient strabismus or nystagmus or projectile vomiting may develop within a few hours. Occasionally more serious reactions may occur, chief of which are convulsions, opisthotonus, general muscular rigidity or sudden high fever. Rarely marked drowsiness followed by a prolonged sleep occurs after intrathecal streptomycin. Muscle flaccidity with complete loss of superficial reflexes may be evident for 24 hours or more.

Results of Treatment with Streptomycin and Promizole. Since December, 1946, 21 consecutive cases of tuberculous meningitis have been treated; 16

survive. Thirteen of the survivors have completed streptomycin therapy and are continuing with promizole. All cases which have been treated are listed in Table 1 with their status as of July, 1949. Discussion of the physical and mental condition of the survivors will be limited to those who have completed streptomycin therapy and hence have been observed for a minimum period of 6 months; that is, the 13 survivors of our first 18 patients.

In most cases there was little apparent response to therapy during the first weeks of treatment. Even when streptomycin and promizole were begun during the first stage of general symptoms, the children often developed the neurological picture of the second stage of meningitis and under treatment this phase lasted from 2 weeks to several months. Even the third or comatose stage of the disease developed under treatment in cases which ultimately recovered. Patient 5 developed meningitis while he was in the hospital under observation for primary tuberculosis. During the 3rd and 4th weeks of the disease he became blind, then deaf, and led a vegetative existence. By the 4th month of therapy, vision and hearing were restored; there was slow but progressive improvement and on discharge to his home he seemed entirely normal both physically and mentally. Some children seemed to have completely recovered from meningitis even before the 6 months of streptomycin therapy were completed. Often, however, convalescence was prolonged. Patient 6 showed clinical evidence of tuberculous encephalitis as well as meningitis. During the 3rd month of treatment she developed difficulty in swallowing and a lagging speech, associated with coarse tremors of the extremities. By the end of 6 months of streptomycin therapy she was clear mentally but extremely weak and emaciated; after many months of further convalescence she has finally become fully rehabilitated.

As noted by Cairns and others[1], spinal fluid in patients with tuberculous meningitis treated with streptomycin tends to return to normal earlier in children than in adults. Spinal fluid proteins remained elevated in only 5 patients at the time streptomycin therapy was finished; 2 of these relapsed. Spinal fluid sugar usually returned to normal within a few weeks. Cells showed great variations in numbers but returned to normal in all survivors before streptomycin intramuscularly had been discontinued.

Of the 13 survivors who have completed treatment, 5 had paralyses of one or more extremities during the 1st month of meningitis. Neurological weaknesses persist in 4 children; 2 have hemiplegia, 1 child has recovered complete use of his arm but still has a weakness of his leg; 1 child has a residual foot drop. These 4 children (Cases 8, 9, 10 and 15) are all able to walk; they are improving steadily under orthopedic supervision and physiotherapy. One child (Case 2) developed internal strabismus during the 1st week of therapy and this condition persisted for 6 months. Electroencephalograms have been normal except in Cases 3, 8 and 10; these show localized changes.

None of our surviving children shows evidence of mental deterioration. The results of psychometric examinations have been within normal limits.

Relapses. Relapses occurred in 3 cases (3, 8 and 10), the only children in whom abnormal electro-encephalograms were obtained. In each case the first indication of a return of the meningitis was a change in the chemistry of the cerebrospinal fluid obtained as part of a routine examination during the first weeks after combined therapy was discontinued. The spinal fluid changes, consisting of a lowered sugar

and increased protein content, were found 25 to 45 days after the last dose of streptomycin and at the time of diagnosis were not associated with neurological signs. In each case tubercle bacilli fully sensitive to streptomycin were recovered from the first spinal fluid which showed abnormal chemistry values. Patient 3 began to deteriorate physically in the 4th month of his relapse and died shortly thereafter of tuberculous meningitis. Tubercle bacilli recovered from the spinal fluid just before clinical meningitis developed were resistant to more than 100 micrograms of streptomycin. Patient 8 after finishing his second 6 months course of therapy relapsed a second time, again about 6 weeks after streptomycin was discontinued and diagnosed only on spinal fluid findings. Tubercle bacilli cultured from his spinal fluid at the time of his second relapse were again fully sensitive to streptomycin. This boy has just completed his third 6 months course of treatment with streptomycin and is in good general condition.

Discussion. Many series of cases treated with streptomycin as the sole therapeutic agent have been published. Reports from the Medical Research Council in England, The Sick Children's Hospital in Paris[3] and the Veterans Administration in the United States[19] gave survival rates of about 37% 4 to 6 months after the initiation of treatment. On further follow-up the percentage of cases surviving is reduced. Recently McDermott[13] stated that sustained recoveries may be obtained in 10 to 15% of cases of tuberculous meningitis treated with streptomycin, with an additional 10% surviving in a badly crippled state. The highest percentage of survivors from tuberculous meningitis have been reported in cases receiving streptomycin combined with a sulfone. In 1947 Cocchi and Pasquinucci[2] reported good results in the treatment of tuberculous meningitis with streptomycin, promin and large doses of vitamin A. Recently Pasquinucci[17] has reported a total of 183 cases with a survival rate of 47%.

From these reports and our experience it would seem that the addition of other tuberculostatic agents to streptomycin is of advantage in the treatment of tuberculous meningitis. Not only is the effect of streptomycin enhanced, but this procedure has been shown to delay or diminish the emergence of drug resistant tubercle bacilli[6]. The role of combined therapy in reducing the incidence of drug resistance cannot be evaluated in our small series of cases of meningitis. We believe that in children promizole is the most valuable drug to supplement streptomycin in the treatment of tuberculous meningitis. It has been shown to cause complete arrest of miliary tuberculosis when used as the sole chemotherapeutic agent. Its relatively low toxicity and its mode of administration permit it to be used for years. Moreover, Pope and Smith[18] have shown that the concentration of para-aminobenzoic acid required to inhibit the bacteriostatic action of promizole is much higher than that required for other commonly used sulfones. This finding may explain in part the difference in therapeutic results obtained with promizole and other sulfones.

The evaluation of results of treatment of tuberculous meningitis must not be made solely in terms of survival. The goal of treatment should be the complete restitution to normal of the affected individual. Early diagnosis is frequently stressed as one of the most important factors in increasing the percentage of survivals of patients with tuberculous meningitis. However, early diagnosis must be combined with prompt and adequate treatment if it is

to accomplish its object, to prevent irreversible changes in the brain and the development of severe hydrocephalus.

Summary. The early diagnosis of tuberculous meningitis is most likely to be made in children already known to be tuberculous, as the most common early complaints may be general symptoms such as fever, vomiting and apathy or drowsiness.

In children not known to be tuberculous, the routine use of a tuberculin skin test in persistent fever or unexplained illness should result in more early diagnoses of tuberculous meningitis.

In the evaluation of the results of chemotherapy it is important that serous tuberculous meningitis should not be mistakenly treated as tuberculous meningitis since the prognosis is not as serious.

The goal of treatment of tuberculous meningitis should be complete restitution to normal.

Early diagnosis combined with prompt and adequate therapy are important factors in attaining this goal.

We report 18 cases of meningitis which have completed treatment with streptomycin and are continuing treatment with promizole given orally. Thirteen children survive 9 to 27 months after the initial diagnosis. All are mentally normal. Four have neurologic residuals, none seriously crippling.

The addition of adequate amounts of promizole to streptomycin would seem to be of advantage in the treatment of tuberculous meningitis.

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MASKED MYOCARDIAL INFARCTION

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The clinical picture of acute coronary artery occlusion with myocardial infarction has been well-known since the original description by Herrick[12], and it is usually rather typical and relatively easy to recognize. There are frequent instances, however, when this condition manifests itself in somewhat unusual ways, or is obscured by the symptomatology of a concurrent disease; and the diagnosis may easily be missed if it is not thought of and if an electrocardiographic study is not made. This is especially true in cases in which there is no pain—a not inconsiderable group of 20 to 40% of all infarctions[1]. As the differential diagnosis is discussed in every textbook of medicine and cardiology, it is not the purpose of this paper to review it in detail, but rather to point out some of the ways in which an actual myocardial infarction may be masked by atypical symptomatology. We feel that this is especially important now that the use of anticoagulants have been developed as a definitive and fairly effective treatment for this condition[18].

In recent months there have been admitted to the Cardiac Division of the Henry Ford Hospital several individuals who have later been proven to have myocardial infarctions, but who have had symptoms and physical signs pointing primarily to other conditions, so that the diagnosis was missed by at least one examiner. Because there is a very high incidence of myocardial infarctions at this hospital, and because it is our practice to take an electrocardiogram on every patient who might possibly have cardiac disease, the errors were soon picked up in all except 1 case. Under other circumstances, however, the proper diagnosis might never have been made, and we, therefore, feel it worth while to report these cases.

In reviewing the subject we found that although there have been frequent individual reports of atypical occlusions and studies of groups of one type or another, an attempt has apparently not been made to classify and describe the various pictures which may obscure the diagnosis of coronary occlusion with infarction. On the basis of recent experience in this hospital, the following admittedly incomplete classification is made, and individual cases of several types will be summarized.

In general, the masking pictures may be grouped under 2 heads—those which result from complications of the infarction itself, and those due to concurrent and independent diseases. It is obvious that there is some overlapping, as in Cases 4 and 6.

Case Reports. Case 1. L.H., a 56 year old white male machinist, was admitted to the Surgical Service on October 26, 1947, complaining of pain and numbness in the right hand and forearm of 4 hours duration. This pain was not preceded by any symptoms suggestive of cardiac disease, except very slight exertional dyspnea for several months previously. On examination there were found typical signs of occlusion of the right axillary artery. No abnormalities of the heart or lungs were noted. The occlusion was treated with

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morphine, ice packs, heparin, tetra-ethyl-ammonium chloride, and stellate ganglion block, and the patient was left overnight. Nearly 24 hours later he was seen by the cardiac consultant, in the meantime having been allowed to feed himself, to go to the bathroom and to be rather active generally. The condition of the arm was noted to be about the same as before. The cardiac rhythm was regular. The heart tones were of good quality, and there were no murmurs or pericardial friction rub. The lungs were clear. The pulse was 68, the temperature 98.6, and the blood pressure 130/86. In spite of the absence of suggestive physical findings, a myocardial infarction was suspected, and an electrocardiogram ordered. The latter was interpreted as indicating a new antero-septal infarction (See Fig. 1). Operation was performed the same evening, and an embolus was removed from the right axillary artery. The arm recovered well, thereafter. The patient was placed on strict bed rest and anticoagulant therapy, and convalescence was uneventful.

CASE COMMENT. This case illustrates the necessity of careful study of the whole vascular tree in all cases of acute arterial embolism. Warren and Linton[17], in their paper on the treatment of arterial embolism, report myocardial infarctions as the source of the emboli in 15 of 98 patients. Conversely,

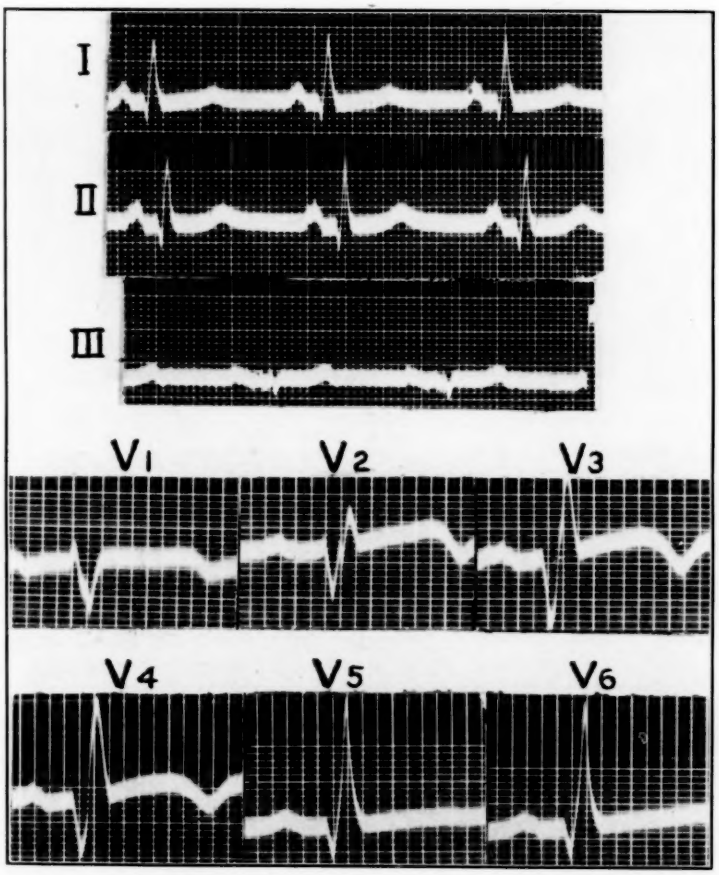

FIG. 1. CASE 1. Oct. 27, 1947. Rate, 64. P-R, .17. QRS, .09. Small Q in Leads 1 and 2. Deep Q wave in V_2 through V_6. Elevation of ST segment from V_2 to V_4. Inversion of T wave V_2 to V_4, and flattening of the T wave in V_5 and V_6.

Hellerstein and Martin[11] report that 11.5% of 1605 clinical cases of myocardial infarction developed peripheral emboli. The presence of myocardial infarction may frequently be perfectly obvious; but often, as in this case, it is not and must be looked for. The immediate treatment in the above case would probably not have been altered by an earlier diagnosis, but the general care of the patient would certainly have been more conservative had the infarction been discovered earlier. At any rate, if the infarct had been persistently overlooked, disastrous results might have ensued. In cases of peripheral emboli of obscure origin, myocardial infarction must be searched for.

Cerebral vascular accidents may also occur following myocardial infarction with mural thrombus formation. One such case has been seen in our hospital in recent years, occurring in a rather young man and presenting a difficult

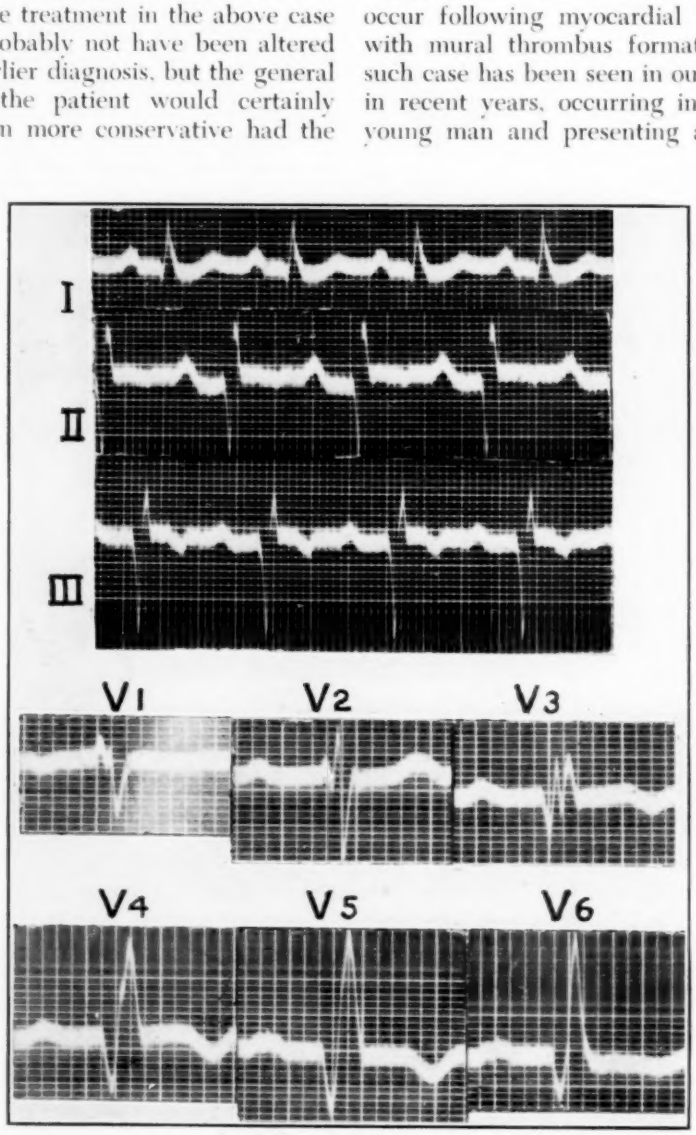

FIG. 2. CASE 2. Sept. 7, 1948. Rate, 88. P-R, .22. QRS, .10. Deep Q in Leads 2 and 3. Elevation of ST segment and inversion of the T wave in Leads 2 and 3, and depression of the ST segment in Lead 1. Deep Q in V_3 through V_6. Inversion of the T wave V_3 through V_6.

etiological problem until the infarct was discovered. Dozzi[9] found 8 such unsuspected infarctions in his series of 66 patients with cerebral vascular accidents.

Another important type in the embolic group, under the heading of complications of the infarction, is that in which the picture of pulmonary embolism presents itself. This type is illustrated by Case 2, the second admission of the same patient described in Case 1.

Case 2. L.H. was followed in the Out-Patient Department and got along well for 11 months. On September 7, 1948, he came into the Clinic with the story that 4 days before he had noted a gradual onset of aching, substernal pain increasing in severity and spreading throughout the anterior chest and aggravated by respiration. The pain was also noted posteriorly and was accompanied by some dyspnea, but he was able to sleep at night. The next day he began to cough up clumps of bright, red blood, and hemoptysis had persisted until he came to the Clinic. When examined, he appeared acutely ill, and was sweating and breathing jerkily. There was no cyanosis, and arterial circulation in the extremities was adequate. The heart was not enlarged, but there were cycles of protodiastolic gallop at a rate of 96 per minute. Blood pressure was 120/78. Moist rales were heard at both lung bases, more on the left. There was no pleural or pericardial friction rub. On the basis of the history and findings, it was felt that the patient had had pulmonary embolism with infarction of the lung, either from an old mural thrombus, or a new one, due to a new myocardial infarction.

An electrocardiogram showed findings as in Fig. 2. A diagnosis of a new posterior myocardial infarct, plus the old antero-septal one, with a new mural thrombosis and pulmonary embolism was made. Subsequent electrocardiograms and the clinical course confirmed this diagnosis.*

Case Comment. During the past few years so much emphasis has been placed on phlebothrombosis complicated by pulmonary embolism that it has come to seem a relatively common disease. When pulmonary embolism occurs, attention is usually directed toward the leg veins, and rightly so. It must be remembered, however, that such embolism not at all infrequently occurs following myocardial infarction, and that the latter must be kept in mind, even if the symptoms do not indicate it. Denham and Smith[8] found in a review of the literature that 22½% of 967 autopsied myocardial infarcts showed complicating pulmonary infarcts and that 7.2% of 540 clinical cases had clinical pulmonary infarctions. Hamburger and Saphir[10] in 1930 discussed the differential diagnosis of pulmonary infarction and coronary thrombosis and recommended that myocardial infarction should be looked for in every case of or picture of pulmonary embolism. Whether the embolus actually arises from the mural thrombus or from the leg veins following myocardial infarction need not concern us here. The important thing is that serious heart disease is present and that the proper therapy must be instituted for it, in addition to the treatment of the lung complication. The electrocardiogram usually reveals the answer, although careful attention to clinical findings often provides a clue.

Pulmonary edema following silent myocardial infarction presents a clinical picture so dramatic and so well-known that we need not dwell on it here. What is not so widely recognized, however, is that the picture of cardiac dilatation with clinical shock and the syndrome of generalized myocardial failure, especially when it is predominantly "right sided" failure, may also follow such an infarction. This general picture appears so frequently as a terminal stage of rheumatic heart disease that it is sometimes forgotten that

* It is interesting to note that just 2 weeks after discharge from the hospital for this episode, this same patient had a third coronary occlusion with infarction, this time with a typical clinical picture.

infarction may be the precipitating factor. The following case, in which the diagnosis was not made until the post mortem examination, illustrates the pitfalls which lie in the path of one who too readily makes the most obvious diagnosis in such a situation.

CASE 3. G.C., a 25 year old Negro male, was admitted on November 1, 1948. He was so ill that an adequate history was not obtained, but he stated he was well until 6 months previously. At that time while walking down the street, he had developed a burning anterior chest pain without radiation, which lasted 25 to 30 seconds. The pain subsided and he felt nothing more until, on awakening the next morning, he was weak and dyspneic. He was seen by his doctor who told him that he had heart trouble and advised him to "take it easy." He did not work following this but he was able to do easy chores around his home. Six weeks prior to admission he became more dyspneic, and was admitted to another hospital where he was treated with digitalis and "injections for water." He did not improve, and for about a week prior to coming to Henry Ford Hospital he had not been out of bed. During the latter period, he had some chest pain every day; some dyspnea, ankle edema and nausea. In the last 2 days

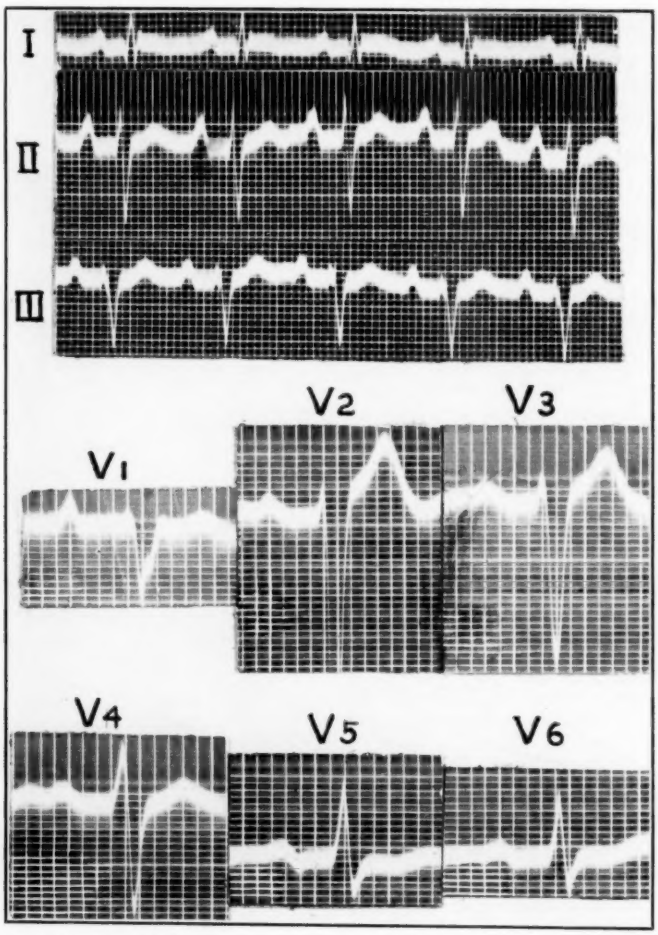

FIG. 3. CASE 3. Nov. 2, 1948. Rate, 97. P-R, .20. QRS, .08. Slight elevation of the ST segment in Lead 1 and flattening of the T wave. Small Q in Lead 1. Deep S in V_2. Low R in V_3. Depression of the ST segment, V_5 and V_6.

of his stay he had had, at the former hospital, fever up to 101°, sweats and 3 small hemoptyses. He was told that he had rheumatic heart disease. Finally he signed a release and came to our hospital.

He denied joint disease or fever as a child, but did say that he had had occasional spontaneous nosebleeds. He denied any primary or secondary syphilitic lesions, but had received bismuth injections for several months because of a positive Wassermann.

On admission he was found to be emaciated and acutely ill. He was moderately orthopneic and the extremities were cold and clammy. The optic fundi were normal and there was no icterus. The lungs were clear to percussion and auscultation. The apex impulse was in the anterior axillary line and was heaving in character. There was a rather loud apical systolic murmur, heard also at the aortic and pulmonic areas. There was a protodiastolic gallop. Diastolic murmurs were thought to be heard by some, but not by others. The liver edge was felt 10 cm. below the xiphoid cartilage, and was tender. There was 2+ ankle edema. The pulse rate was 120 and regular. Blood pressure was 115/90. Hemoglobin was 16.3 gm., RBC 5.13 million, WBC 8650 with 73% neutrophils. Kline test was 4+, Kolmer 20,000, Kahn 2+. Chest roentgenograms revealed cardiac enlargement and congestive changes in the lung fields. It was thought that on the basis of the history and findings the patient had rheumatic heart disease, although an exact diagnosis of the valvular lesions was not attempted. An electrocardiogram (Fig. 3) was not thought to alter the diagnosis. The patient's course was progressively downhill in spite of oxygen, digitalis, morphine and other measures. He continued to cough up blood and the blood pressure became unobtainable. Dyspnea became worse and he died 3 days after admission.

Autopsy. No evidence of valvular disease, although the heart was markedly dilated and 2 infarctions were found on the anterolateral aspect of the left ventricle, 1 new and 1 old. There was marked sclerosis of the coronary vessels with occlusion of the left circumflex branch. No evidence of cardiovascular syphilis was found.

CASE COMMENT. This case was remarkable in several ways. First, the youth of the patient was misleading; secondly, he was a Negro; thirdly, the history and physical findings were certainly not typical of myocardial infarction. Even the electrocardiogram, although compatible with such a diagnosis, was certainly not diagnostic of it. His case is presented not because it is typical, but simply to illustrate that such a picture can be produced by infarction, and as a reminder that the latter must be kept in mind in any case presenting the syndrome of generalized myocardial insufficiency.

Cardiac arrhythmias occurring without obvious cause can also not be disregarded or classed indiscriminately as idiopathic. Myocardial infarctions may sometimes manifest themselves solely by the onset of ventricular tachycardia, frequent extrasystoles, auricular fibrillation or flutter, heart block, or some of the rarer forms of disturbances of rhythm[14]. The arrhythmia and its treatment should not cause the clinician to omit a search for the cause of the irregularity. It may be a coronary occlusion.

CASE 4. G.M., a 47 year old white male, bowling alley manager, was admitted to the hospital on January 13, 1949, complaining of persistent nausea and vomiting of 3 days duration, and of dyspnea becoming progressively worse for 2 days. The symptoms began very suddenly with a feeling of weakness, ashen color, and apprehension. He had had no pain at all, except for some backache for 24 hours prior to admission. On the first day of his illness he was seen by a physician who told him that he had intestinal obstruction, but did not examine his chest. No therapy was recommended. He had not urinated for about 12 hours prior to admission.

There was no past history of hypertension, angina or other vascular disturbances. He said that he had had "flu" about a month before, and this had left him with a slight cough.

On examination, the patient appeared to be very ill, with marked cyanosis and orthopnea. Temperature was 98.6 F., pulse 160 and blood pressure 92/70. The relative cardiac dullness extended 13 cm. from the midsternal line. Heart tones were of poor quality, but the rhythm was regular and no murmurs or gallop were heard. There were many moist rales in both lower lung fields. The abdomen was moderately distended and the liver edge

was felt 3 cm. below the right costal margin. Neck veins were moderately distended. Radial pulses were not palpable. There was no edema. Pressure on the carotid sinuses produced no change in the cardiac rate or rhythm.

On the basis of the history and physical examination, it was judged that the patient had a cardiac arrhythmia of undetermined nature with myocardial insufficiency, and probably an underlying infarction. The electrocardiogram (Fig. 4) revealed evidence of a ventricular or nodal tachycardia with interference dissociation, and an anterior myocardial infarction superimposed on right bundle branch block. The arrhythmia was finally converted with large doses of quinidine and the signs of heart failure cleared slowly with appropriate therapy.

Fig. 5, taken after the conversion of the arrhythmia, shows infarction even more strikingly. Anticoagulant therapy was begun at admission and continued after the other measures became unnecessary.

Case Comment. This case illustrates an arrhythmia of unusual type, as the presenting manifestation of a coronary occlusion with myocardial infarction. It also graphically points out the folly of diagnosing abdominal disease without adequate study of the chest. The latter point, *i.e.*, the primarily digestive symp-

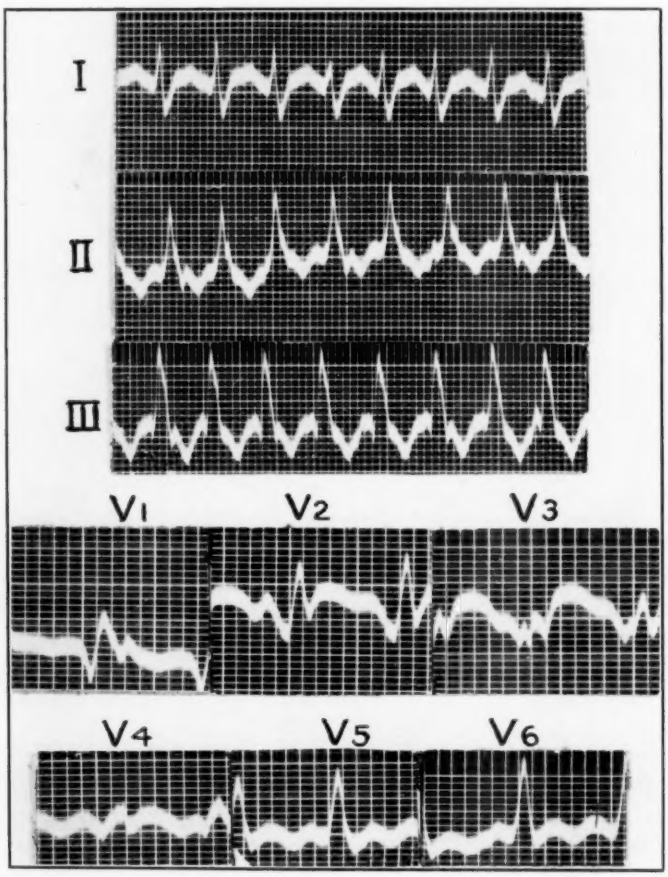

Fig. 4. Case 4. Jan. 13, 1949. Ventricular rate, 200. Auricular rate, 136. QRS, .12. Ventricular tachycardia with interference dissociation, the impulse probably arising from a focus in the left ventricle. The distortion of the complexes produced by the ventricular tachycardia is such that the infarct cannot be localized in this tracing.

toms, introduces the next classification of masking factors due to complications of the infarction.

Not only may the complications of myocardial infarction be vascular, but they may also involve other organ systems, chiefly the gastrointestinal. Theoretically, this group should not cause too much difficulty, since it is well known how closely the digestive tract and the heart are allied, and since there are usually fairly definite signs pointing to the heart as the source of trouble. Occasionally, however, the problem becomes more complex, and suspecting myocardial infarction as the cause of the digestive symptoms calls for real clinical acumen. Brooks[4] called attention to this in 1932. He pointed out that myocardial infarction can produce almost any digestive symptom complex and can stimulate a great variety of gastrointestinal diseases. Case 5 was such a problem.

Case 5. A.C., a 46 year old Syrian grocer, was admitted on October 28, 1948, complain-

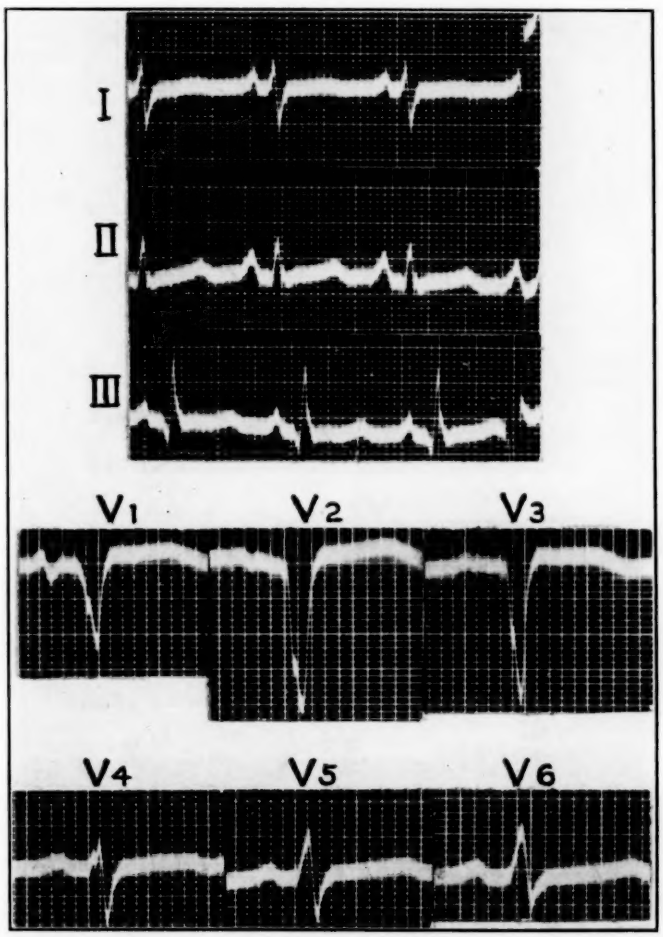

Fig. 5. Case 4. Jan. 20, 1949. Rate, 83. P-R, .18. QRS, .10. Flattened T wave in Lead 1. Slurring and notching of the QRS in all leads. Small Q in Lead 3. Absent R wave, V_2 and V_3. Diphasic T wave, V_3.

ing of a pain high in the abdomen. He stated that about 2 weeks before, following a very heavy meal, he had noted high epigastric discomfort and a feeling of fullness and compression followed by sweating but no radiation of the pain, palpitation or dyspnea. The pain was relieved in about 5 minutes by belching and he had no further difficulty until the day before admission. At this time, the pain again followed a heavy meal, but recurred 3 times, being relieved each time by eructations of gas. He felt perfectly well then and was in no distress at the time of admission. Some 5 years before he had had an attack of severe chest pain coming on at rest and radiating to the left arm. This was diagnosed by his family physician as angina pectoris but no treatment was carried out and there was no recurrence, in spite of an active life. He denied previous digestive symptoms.

On examination he appeared well, although somewhat obese and apprehensive over the examination. Pulse was 100. Blood pressure was 130/90 and the temperature 98.6 F. The heart was enlarged. The tones were normal and there were no murmurs, gallop or rub. The chest was clear to percussion and auscultation. The abdomen was not remarkable. On the basis of the occurrence of the pain after over-eating, the lack of effort angina, the

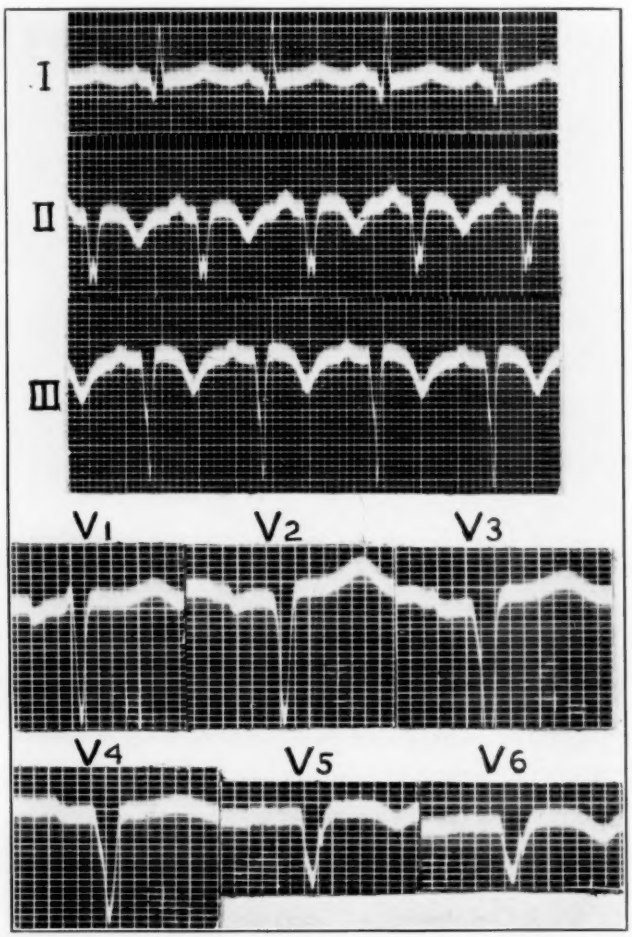

FIG. 6. CASE 5. Oct. 28, 1948. Rate, 94. P-R, .16. QRS, .08. Left axis deviation with deep QS in Leads 2 and 3, and a small Q in Lead 1. Deep inversion of the T wave in Leads 2 and 3. Slight elevation of the ST segment in Leads 2 and 3. Absent R wave V_2 through V_6. Inversion of the T wave in V_5 and V_6.

reported distention and gas, the patient's age and apparent good condition, and the lack of cardiac findings, it was thought that his symptoms were entirely digestive in origin and probably functional. However, there was just enough in the story to arouse suspicion of coronary disease, and an electrocardiogram was done prior to any gastrointestinal studies. This electrocardiogram revealed the rather surprising findings shown in Fig. 6. On the basis of this electrocardiographic picture, a diagnosis of old anterior and new posterior myocardial infarctions was made, and therapy was instituted. On the following day the patient developed some fever and his sedimentation rate was 22 mm. per hour. The white blood count was never above 6050.

CASE COMMENT. If this patient had been 60 years old, a diabetic, or hypertensive, or acutely ill when seen, or if the pain had been higher and not relieved by belching, the problem might not have been difficult. As it was, and frequently is, a careful evaluation of the story and intelligent use of the electrocardiograph were the only ways to solve the puzzle. Various authorities[16] have noted that abdominal pain is not infrequently a symptom of coronary occlusion, and this should be kept in mind. It is our belief that whenever there is the slightest suspicion of a cardiac origin for upper abdominal pain or distention, or nausea and vomiting, an electrocardiogram should be taken, using all the precordial leads as well as the standard ones. It is only in this way that there can be avoided the rather grave error of passing a stomach tube or doing a proctoscopic examination, or barium enema roentgenogram on a patient with a fresh myocardial infarct.

The second major group of masked myocardial infarctions are those in which the major diagnosis is obscured by some concurrent disease. The number of such diseases is, of course, large and we shall discuss briefly only the main ones.

Gastrointestinal conditions are the major cause of confusion in this second group. Not only may gastrointestinal symptoms be precipitated by coronary occlusion but there may be some digestive disease already present, the symptoms of which may divert all suspicion from the heart. Many authors have discussed the differential diagnosis between gall bladder disease and coronary disease, and this is difficult enough, but there may be pitfalls even when the differentiation has been accomplished. The diagnostician may find that his patient does have gall bladder disease, only to learn later that he has also had a silent coronary occlusion which has simply aggravated the prior condition. This was noted so often that Campbell[7] in 1936 attempted to postulate an etiological relationship between the 2 conditions. Acute pancreatitis is another gastrointestinal disease which may give trouble, and, of course, peptic ulcer is a frequent source of difficulty. Cabot, Case No. 31262[6], was that of a patient with a bleeding ulcer who was treated for this condition and it was only on autopsy that old and new myocardial infarcts were found. Brooks[4] described similar patients. We have recently had several patients[13] whose presenting findings were hematemesis or melena and who had old ulcers and new myocardial infarctions, the latter apparently in some way precipitating the acute bleeding. Even a patient with an irritable colon, who has had almost regular upper abdominal distress, may have a coronary occlusion missed because the examiner thought his new pain was just a variation of the old.

Closely allied with this group and often indistinguishable from it is the group of neurotics, whose symptoms, nearly always digestive, have such a high functional content that they mislead all but the most astute observers. Such is Case 6.

CASE 6. E.M., a 58 year old white female was admitted to the Henry Ford Hospital on

November 28, 1948. She stated that during the past month she had had 6 or 7 attacks of a feeling of pressure under the sternum and in the epigastrium. The first of these attacks occurred about an hour after she had raked some leaves and was accompanied by a feeling of weakness in the arms but no actual pain there. There was no dyspnea, or palpitation and the pain subsided spontaneously after a few minutes. The second attack occurred while she was walking to church and was similar in nature. She visited a local doctor who told her that she had angina pectoris but took no electrocardiogram. She was alarmed by this diagnosis and proceeded to read all she could find on the subject of coronary disease, becoming more alarmed with each article she read. Subsequently, she had several more attacks, usually coming on at rest, usually after meals. She then saw 2 other doctors, both of whom told her she had "nothing but nerves." She stated that she had been constipated for many months, was quite subject to "gas and bilious attacks" and took cathartics daily. There had never been any history of dyspnea, palpitation, ankle edema or hypertension.

On examination, it was noted that the patient was very nervous and apprehensive; so agitated, in fact, that she was unable to answer questions coherently. Otherwise, she did not appear in any distress. General physical examination was non-contributory. The pulse was 100; blood pressure was 125/72. Temperature was 98.6. Cardiac dullness extended 7½ cm. from midsternum. The mitral first sound was split. No murmurs or friction rubs. The liver was palpable on inspiration and slightly tender. There was slight generalized abdominal tenderness. The lungs were clear to percussion and auscultation. On the basis of the history and physical examination, it was thought that this woman

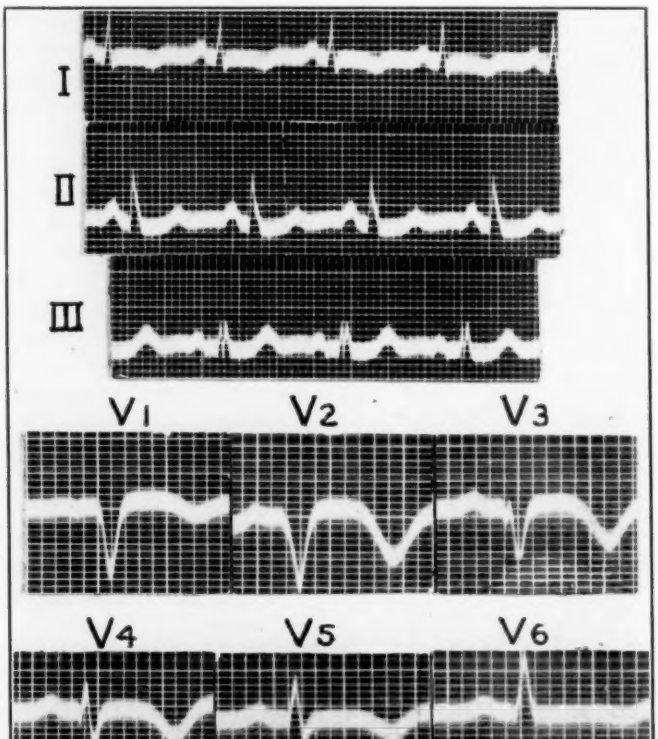

FIG. 7. CASE 6. Nov. 28, 1948. Rate, 91. P-R, .16. QRS, .08. T wave inversion in Lead 1. Loss of the R waves in V_2 and V_3. Small Q wave in V_4. Inversion of the T wave, V_2 through V_6.

had a rather severe anxiety neurosis, an irritable colon, and perhaps some gallbladder disease. Since the pain was highly suggestive of angina, however, an electrocardiogram was ordered. The latter revealed the findings shown in Fig. 7, and a diagnosis of coronary occlusion with anteroseptal myocardial infarction was made.

CASE COMMENT. That neurotics may be really ill and even die is a fact too often forgotten[5]. When the examiner is confronted with a tense, high-strung, apprehensive individual with a multiplicity of symptoms, a vague story, and the whole thing, as in this case, colored by a previously accepted diagnosis, he may be prone to overlook the clues which will lead him to the cardiac disease. This case illustrates graphically the important but frequently neglected principle that almost no chest pain, however bizarre in location or unusual in circumstance, can safely be ignored. If there is the remotest suspicion of coronary disease, electrocardiograms should be made. This is especially true in the so-called neurocirculatory asthenias, where the distinction between functional and organic cardiac pain is often difficult.

Dyspnea, along with pain and a collapse state has long been associated with the diagnosis of coronary occlusion. Dyspnea is, however, not always easy to evaluate or to classify etiologically. The picture of real cardiac asthma is a fairly typical one, and causes a search for cardiac disease; but when the patient's dyspnea is that of a bronchial asthma[3] or pneumonia, the problem becomes less simple, and the underlying heart disease may be unsuspected. Similarly, lung diseases can cause chest pain, and chest pain is not always perfectly typical of either cardiac or pulmonary pathological processes. The presence of a concurrent lung disease may so becloud the issue that the possibility of myocardial infarction is not thought of. Case 7 is illustrative.

CASE 7. A 53 year old white male was admitted to the hospital October 12, 1948, complaining of cough, dyspnea and chest pain. He stated that he was well prior to 6 weeks before admission, when he developed exertional dyspnea, cough and occasional episodes of nocturnal dyspnea. He had never had any pain on exertion or excitement. The day before admission, he had had some nasal congestion, sore throat and general malaise. About midnight he developed a moderately severe pain in the upper left chest, stabbing in character, non-radiating, and not accentuated by deep breathing or cough. This pain persisted for several hours and he became somewhat dyspneic, but the shortness of breath seemed to be relieved by lying flat. After lying for some hours with his hands behind his head, he had a sensation of numbness and coldness of the hands and some aching in the antecubital fossae. The pain lessened, but was still present at the time of admission. The cough had increased and was moderately productive of thick yellow sputum.

The past history revealed that he had had a chronic moderately productive cough for many years with occasional bouts of bronchitis. He had worked in a foundry for 17 years (1919 to 1936). He had never had any heart disease, angina or suggestive cardiac symptoms.

On examination he did not appear acutely ill. The temperature was 99.F. The pulse was 100. Blood pressure was 110 systolic and 90 diastolic. He was slightly dyspneic and an expiratory buzz was audible at the open mouth. The neck veins were not distended. The relative cardiac dullness extended 10 cm. from the midsternal line. The cardiac rhythm was regular, with a rather faint presystolic gallop. No murmurs were noted. The lungs were resonant throughout. Loud expiratory wheezes were heard in both lungs, with some bubbling rhonchi. There were a few persistent moist rales in the left base. The liver was not felt and there was no edema. The clinical impression was acute bronchitis with a possible localized pneumonitis, superimposed on chronic pulmonary fibrosis. Myocardial infarction was considered, but felt to be unlikely. However, an electrocardiogram revealed the findings shown in Fig. 8. The sedimentation rate was 37, and the white blood count 8000, with 73% neutrophils. Roentgenograms of the chest revealed a hilar enlargement on both sides, increased bronchovascular markings, bilateral fibrosis and some nodulation.

On the basis of the electrocardiographic findings, diagnosis was made of acute coronary occulsion, with anterior myocardial in-

farction superimposed on an old posterior infarction. The infarction was treated with anticoagulants, but it was also found necessary to give penicillin parenterally and by inhalation to control the cough, fever, and expectoration.

CASE COMMENT. The persistent pain, and the gallop rhythm as found on the physical examination here should have provided very strong clues to the diagnosis; but the very obvious presence of pulmonary disease was misleading. One diagnosis was easily made and it seemed to be sufficient. Whether the pulmonary infection had any etiological connection with the infarction or even with the dyspnea is not so important. The essence of the matter was that definite cardiac symptoms and signs could not be ignored even though they were questionably explainable on the basis of the obvious disease.

In considering the concurrent conditions which may mask the myocardial infarct, it is also wise to remember that any surgical procedure, no matter what the reason for it, may provide

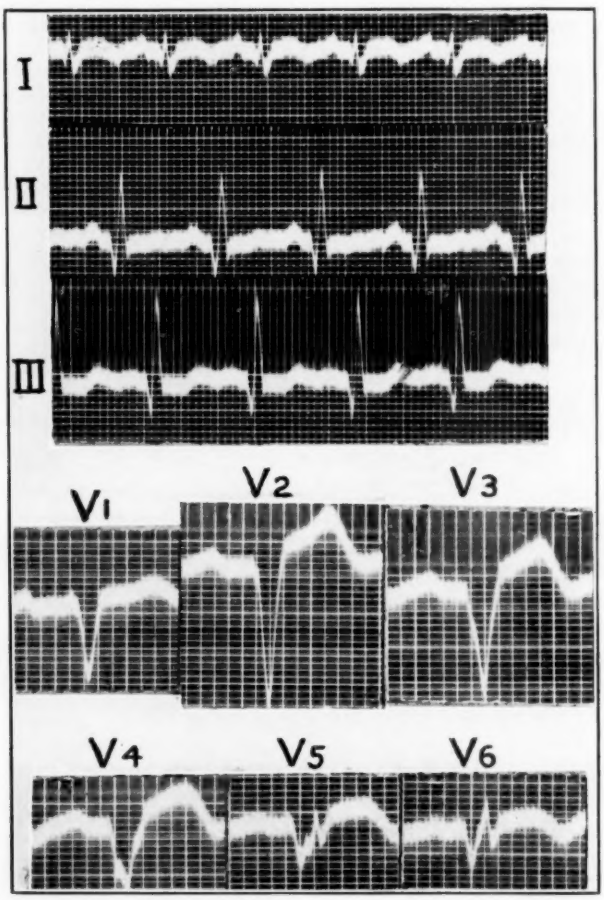

FIG. 8. CASE 7. Oct. 12, 1948. Rate, 110. P-R, .13. QRS, .10. Deep Q waves in Leads 2 and 3. Small Q in Lead 1. Slight elevation of the ST segment in Lead 1. Slight depression of the ST segments in Leads 2 and 3. Inverted T wave in Lead 1. Flattened T wave in Lead 2. Loss of R waves in V_2 through V_5. Deep Q wave in V_6. Elevation of the ST segment in V_2 through V_6. T wave diphasic in V_2 through V_5, and inverted in V_6.

a screen behind which severe cardiac disease may hide. When the clinical picture of collapse or shock occurs postoperatively, it is apt to be ascribed to hemorrhage or to some other surgical complication. It may be forgotten that silent myocardial infarctions can and do occur in such patients, particularly in the older group. We have found this to be particularly true in the age group in which urological surgery is common. Unless the reason for the fall in blood pressure is obvious, an electrocardiogram and study of the cardiac status is indicated. In 1931, Menard and Hurxthal[15] pointed out the relatively frequent occurrence of such painless infarctions as postoperative complications and warned of the danger of overlooking them.

Summary. It has been pointed out that coronary occlusion with myocardial infarction does not always present a typical clinical picture. The diagnosis may be masked in various ways, and a short classification of the masking factors based on recent experiences and the literature has been presented. The masking factors have been classified into:

1. Infarctions masked by complications of the condition itself. A. Vascular complications. 1, Peripheral emboli; 2, cerebral emboli; 3, pulmonary emboli; 4, congestive heart failure; 5, cardiac arrhythmias. B. Gastrointestinal symptoms.

2. Myocardial infarctions masked by concurrent disease. A. Gastrointestinal conditions. B. Neuroses. C. Pulmonary diseases. D. The postoperative state.

Illustrative cases have been presented.

Conclusions. 1. The diagnosis of myocardial infarction is particularly important now that there is an effective treatment for the condition.

2. There must be a high index of suspicion for the presence of myocardial infarction in a large and varied number of symptom complexes.

3. The clues which point in the direction of heart disease must be followed carefully, no matter what the general picture may be.

4. The electrocardiogram is an indispensable aid in the diagnosis or the exclusion of myocardial infarctions in questionable cases.

The author is indebted to Dr. F. Janney Smith for his advice and criticism in the preparation of this paper.

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PENICILLIN IN THE TREATMENT OF DIPHTHERIA

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One of the first bacterial pathogens which was found to be sensitive to penicillin by Fleming[8] was *Corynebacterium diphtheriae*. Experimental investigations of this effect both *in vitro* and *in vivo* since that observation have produced widely varying results. The *in vitro* sensitivity of strains of the organism which have been studied, shows great variability among the individual strains. Ercoli, Lewis and Moench[7] reported that over 1 unit per ml. was required to inhibit growth of their test strain. Young and Mood[22] reported *in vitro* sensitivities ranging from 0.004 units per ml. to 0.06 units per ml. In testing 30 different strains of *C. diphtheriae*, Long[14] found that from 0.004 units per ml. to 0.02 units per ml. were required to inhibit growth. McDaniels[16], testing stock cultures of *C. diphtheriae*, found sensitivities of from 2.5 units per ml. to 649 units per ml. The *in vitro* sensitivity of 348 strains of *C. diphtheriae* examined by Buxbaum, *et al.*[3] ranged from 0.25 units per ml. to as high as 10 units per ml.

It seems evident that there is general agreement that diphtheria organisms are sensitive to penicillin, but that the degree of this sensitivity recorded in the literature covers a very wide range. The varying techniques used by the several authors in determining sensitivity accounts for some of this wide range. However, the clinician can draw few conclusions from *in vitro* experiments as to the serum penicillin concentration expected to affect clinical diphtheria.

In vivo experiments have been few in number, but have demonstrated that the fatalities in guinea pigs inoculated with *C. diphtheriae* could be prevented by penicillin treatment[7,22].

The experimental demonstration of the sensitivity of diphtheria organisms to penicillin has been followed by a number of clinical reports. Unfortunately, many of these were based on so few patients that generalizations are not warranted. Table 1 presents chronologically, a brief summary of the case material reported up to the date of preparation of this paper, including the studies made on the treatment of persistent carriers with penicillin. It can be seen from this table that a number of reports were based on 1 or 2 patients, and that few of the reports included studies on control patients treated at the same time with antitoxin alone. Without giving a detailed review of all the individual reports, there are several important points to be derived from some. Long[15] and Harries[9] have

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TABLE 1.—SUMMARY OF REPORTS ON THE USE OF PENICILLIN IN DIPHTHERIA CASES AND CARRIERS

Author	*Year*	*Penicillin Route*	*Number of cases*	*Good Results*	*Number of Carriers*	*Good Results*	*Controls*	*Remarks*
Thrift, G. N.[19]	1945	Local			1	1	0	Failure with IM route
Symons, A. D.[18]	1945	IM	1	1			0	Clinical impression of improvement.
Archer, N.[1]	1945	IM	1	1			0	Mixed infection—Hem. strep. and Vincents.
Berman, B. R. & Spitz, S. H.[2]	1945	Local			10	10	0	
Skinner, J. W.[17]	1945	IM	28	16				
McDaniels, H. E.[10]	1945	IM	1	0				Ulcer-organism very resistant
Christie, A. B. & Preston, J. C.[4]	1946	IM and Local	2	1			0	
Kocher, R. A. & Siemsen, W. J.[12]	1946	Local			31	23	0	Lozenges
Dodds, R. J.[16]	1946	IM	13	13			13	No effect on membrane
De M. N. *et al.*[5]	1947	IM	27	27			0	No antitoxin used.
Weinstein, L.[21]	1947	IM	26	23			12	
Weinstein, L.	1947	IM			10	10	0	
Karelitz, S. *et al.*[11]	1947	IM	80	72			42	
Karelitz, S. *et al.*	1947	Local	21	2			42	
Karelitz, S. *et al.*	1947	IM			14	10	0	
Karelitz, S. *et al.*	1947	Local			21	10	0	13 had had previous IM penicillin
Long, D. A.[15]	1947	IM	6	6			0	
Levy, A. J.[13]	1948	Local			4	4	0	3 with lozenges 1 with spray
Walker *et al.*[20]	1948	IM	1	0			0	Fatal case treated with Penicillin, streptomycin and antitoxin.

stressed the importance of the effect of penicillin therapy on the other bacterial pathogens often complicating clinical diphtheria. The beneficial effect of the eradication of hemolytic streptococcus, for example, could conceivably produce, through local and systemic effect, the impression of improvement. Archer[1] presents such a case complicated by hemolytic streptococcus and Vincent's organisms who showed marked clinical improvement during penicillin therapy.

Almost all the investigators have stressed that penicillin therapy has no effect on the toxic component of diptheria. The only reported study which involved a statistically large enough group of patients and which included control patients who received only antitoxin, was that of Karelitz *et al.*[11]. These authors found as many toxic complications in the penicillin-treated patients as in the control group. Several authors[6,11] have noted the absence of any effect of penicillin therapy on the appearance of the membrane.

There have been only 3 investigations which have included a large group of patients bacteriologically studied[11,21,17]. Of these studies, the report of Karelitz *et al.*[11] is most complete. These authors found that the principle effect of penicillin therapy was the reversion of the cultures to negative earlier in the patients treated with penicillin and antitoxin than in the control patients given antitoxin only. Studies on the penicillin therapy of persistent diphtheria carriers have been reported by several authors[2,11,12,13,19,21] and there seems to be general agreement that penicillin, especially when applied locally in the form of spray or lozenges, is effective in terminating the carrier state. Two of these reports[13,19] have been based on such small numbers of patients, however, that the results are probably less valid.

The study of De, Chatterjee and Ganguli[5], based on 27 patients treated with penicillin and without antitoxin, was not adequately bacteriologically controlled. The authors concluded that

antitoxin was still advisable but that penicillin represented an important and economical adjunct.

The report of McDaniels[16] is mentioned to stress the importance of the resistance of some strains of *C. diphtheriae* to penicillin. In this case a diphtheritic ulcer failed to respond to penicillin therapy and the organism was found to be resistant to 640 units per ml.

Summarizing the published literature, it could be said that despite a number of enthusiastic reports of the penicillin therapy of diphtheria based on small and uncontrolled series of patients, there is adequate evidence that penicillin therapy can shorten the length of time over which the organism can be cultured from the patient but that the antibiotic therapy has no effect on the incidence or degree of toxic complications. The penicillin therapy of the carrier state seems to depend more on local application of the antibiotic.

The present investigation was undertaken in an effort to determine whether penicillin therapy could be evaluated from the experience with a number of cases of diphtheria treated on the contagion wards of a large hospital over a period of years.

Material and Methods. The cases available for study comprised all patients who were diagnosed as having diphtheria at the San Francisco City and County Hospital during the years 1942 to 1947, inclusive. From this group, there were taken only those from whom *C. diphtheriae* was cultured early in the course of the disease, and who, if they did not die in the acute phase of the disease, had been followed bacteriologically by frequent cultures. The ages ranged from 1 to 72 years.

Therapy. Over the period included in the study, an increasing number of patients received penicillin therapy in addition to antitoxin. For the total group of patients observed up to the present, however, slightly over ⅔ received penicillin in addition to antitoxin and the remainder received antitoxin only.

The penicillin was given intramuscularly in distilled water or saline solution. The average total dose given in the patients receiving penicillin is shown in Table 2. The average individual schedule was 40,000 units given every 3 hours for a period of 1 week. No patient who received any form of local penicillin therapy is included in the present study. Penicillin therapy was, in every instance, started on the same day of disease on which the antitoxin was given.

TABLE 2.—CLINICAL DATA COMPARING PATIENTS RECEIVING ANTITOXIN ONLY WITH THOSE RECEIVING ANTITOXIN PLUS PENICILLIN.

	Antitoxin only	*Penicillin + Antitoxin*
Total number of patients	62	85
Number of patients with adequate Bacteriological follow-up	49	70
Average age	27.1	29.6
Average day of disease therapy started	5.4	4.6
Average total number of units of antitoxin	36,500	43,000
Average total number of units of Penicillin	0	2.56 Million

All patients received antitoxin on the day of admission to the contagion wards. The average day of disease in which therapy of any sort was started, was comparable in the 2 patient groups (Table 2). The patients getting penicillin received about the same number of units of antitoxin as those not receiving penicillin. The antitoxin was given most commonly by the intravenous route in both groups but there were a number of patients receiving it intramuscularly as well.

Complications. A patient was judged to have a neurological complication if he had evidence of weakness or paralysis of muscles of the extremities or of those supplied by the cranial nerves affected by the toxin of *C. diphtheriae*. A cardiac complication was taken to be present if there was both clinical and electrocardiographic evidence of myocardial damage.

Bacteriological Procedures. All patients in the series had throat and nasal cultures taken on the day of admission and at intervals of 3 to 5 days thereafter, throughout hospitalization. Swabs were streaked on Loeffler slants immediately after being taken and placed in an incubator. These slants were then taken to the laboratories of the City and County of San Francisco for interpretation.

Virulence tests were not done on all cultures made, especially in the earlier years covered by this study. When results of the virulence tests were known to be negative, the case was eliminated from the study.

Results. In Table 3 are presented the clinical data on the cases treated with antitoxin and with antitoxin and penicillin. It can be seen that the mortality rates, when corrected for deaths within 24 hours of admission, are comparable in either treatment group.

TABLE 3.—MORTALITY AND INCIDENCE OF COMPLICATIONS IN THE TWO PATIENT GROUPS.

	Antitoxin only	*Penicillin + Antitoxin*
Total cases	62	85
Total deaths	13	17
Total deaths after 24 hr. hospitalization	6	11
Mortality corrected	9.6%	12.8%
Incidence of myocarditis	(19) 30.6%	(20) 23.5%
Incidence of neurological complications	(5) 8%	(16) 18.8%

The incidence of myocarditis may also be seen to be comparable between the 2 treatment groups. The incidence of neurological complications seems significantly elevated in the group receiving penicillin, but this probably represents a statistical variation based on too few cases in the study. Summarizing this Table, the mortality and incidence of toxic complications seems to be comparable in the 2 treatment groups.

In Table 4 are presented the results of the analysis of the bacteriological data. Only that group of patients on whom adequate bacteriological follow-up was available are considered for statistical purposes. The day of disease on which the culture became negative was taken to be the first day of a negative culture which was followed by consistently negative cultures. The day of disease on which the last positive culture was obtained was recorded as such regardless of the number of days on which negative reports were made and which preceded the positive report. It can be seen that the arithmetic means of these data consistently demonstrate that penicillin therapy shortens the time over which the culture is positive by approximately 7 days. A statistical analysis of all the data from which these means were derived, indicated that the difference between them is significant, being in each case over twice the sigma of the difference between the 2 means.

TABLE 4.—PRESISTENCE OF C. DIPHTHERIAE IN THE TWO TREATMENT GROUPS.

	Antitoxin only (*mean*)	*Penicillin Antitoxin* (*mean*)
Day of disease on which first consistently neg. culture appeared.	24.5	17.7
Day of disease on which last pos. culture appeared.	21.8	13.5

In Fig. 1 the effect of penicillin therapy on the incidence of positive cultures over the course of the disease has been plotted graphically. This Figure compares our results with the data of Karelitz *et al.*[11] and includes as a group of control patients, the data presented by Hartley and Martin[10] on cultures taken from 457 cases of diphtheria treated with antitoxin only. The graph shows that our patients who received antitoxin only show results very similar to those of the group presented by Hartley and Martin[10] and also that the patients who received penicillin seem to fall into an intermediate position between the penicillin treated group reported by Karelitz *et al.*[11] and the controls, with respect to the rate of decline in the incidence of positive cultures. The effect of penicillin therapy on the duration of the positive culture is brought out by comparison between the control groups and the groups receiving penicillin as well as antitoxin.

Discussion. One of the conclusions to be drawn from the presently reported study seems to be that penicillin may

hasten the clearing of the pharyngeal carrier state. This study is comparable, at least in the number of cases presented, to that of Karelitz *et al.*[31] and confirms the latter author's conclusions. It therefore strengthens the proposition that penicillin is of no great value in the treatment of diphtheria. If by statistical study of a large group of cases, the carrier state is found to be shorter by only 7 days, the advantage would seem slight, especially to the individual patient, whose period of bed rest rarely depends on the state of his pharyngeal culture.

Furthermore, the incidence of the most important complications of diphtheria, those ascribed to the toxin, is unaffected by penicillin therapy, not only in the present study, but also in the investigations of others[5,11,15,21], stressing the primary importance of early administration of antitoxin in adequate doses.

Studies on the sensitivity of *C. diphtheriae* to penicillin were not done on the strains responsible for the disease in the patients studied in the present investigation. However, one conclusion as to sensitivity seems to be permissible from the nature of the graph shown in Fig. 1. It will be noted that in the cases treated with penicillin, the graph comparing the incidence of positive culture with day of disease has a slope which differs most markedly from the line representing control cases only from the 5th to the 30th day of disease. Beyond the latter point, the two lines are quite similar. This would imply not only that there are certain patients which, whether receiving penicillin or not, will tend to have a prolonged carrier state, but also that failure of penicillin therapy to affect this tendency perhaps is due to penicillin resistance of the organisms.

This investigation is open to possible

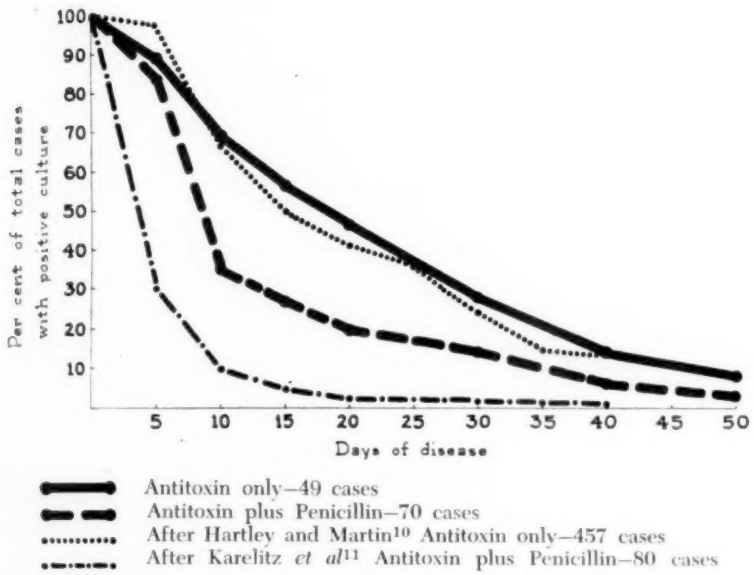

FIG. 1. The effect of penicillin therapy on the incidence of positive cultures, relative to the day of disease, compared with that of control patients treated with antitoxin only. Data from Hartley and Martin[10] and Karelitz *et al.*[11] are included for further comparison.

criticism in regard to two features of the bacteriological technique. Firstly, the Loeffler media employed did not contain any substance such as penicillinase to allow organisms possibly present and not multiplying to make themselves apparent. Also, it is conceivable that the use of additional media such as tellurite would have allowed more positive cultures to make themselves apparent. However, the use of Loeffler's media applies to both control as well as penicillin-treated group, so any effect from this technique would apply to both groups. A second possible criticism is that virulence tests were not done on all cases. However, the failure to carry out a virulence test applies likewise to both treatment and control groups, and therefore the possible inclusion of patients with non-virulent diphtheria-like organisms, while unlikely because of the strict criteria for clinical diphtheria, would not affect comparison between the 2 experimental groups.

The observation made in the present study that penicillin therapy did not have any visible effect on the appearance of the membrane confirms the impression recorded by others[6,11]. It is important to stress also that there was no beneficial symptomatic effect notable in the acute stages of the disease.

Summary and Conclusions. 1. One hundred and forty seven cases of diphtheria, treated with either antitoxin alone, or with antitoxin and penicillin, have been studied.

2. Penicillin therapy in addition to the antitoxin did not affect the incidence of complications or the mortality in these patients.

3. In the patients treated with penicillin, in addition to antitoxin, the diphtheria organisms showed a tendency to disappear from the nose or throat culture slightly earlier than in the patients receiving antitoxin alone.

4. These results are similar to many of the reported investigations on the use of penicillin in diphtheria.

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ANTIGEN TRACER STUDIES AND HISTOLOGIC OBSERVATIONS IN ANAPHYLACTIC SHOCK IN THE GUINEA PIG*†

PART TWO

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In the first part of this study[3] in which we used radioactive labelled bovine gamma globulin as the antigen, we found that lungs of guinea pigs dying in anaphylactic shock had a significant concentration of antigen in the collagenous tissue of the bronchial walls. This collagenous tissue also showed marked vascular congestion and edema which appeared to play the major role in the fatal bronchial obstruction.

The present study was undertaken in order to learn whether the antigen was concentrated in the bronchi during shock because of a specific affinity of the sensitized tissues for the shocking antigen, or because of a non-specific accumulation of protein in the process of edema formation.

We chose egg albumin as the antigen in the present work because the anaphylaxis it produces kills the animal more quickly than that produced by gamma globulin. By studying this rapid anaphylaxis we hoped to learn more about the mechanism of shock, especially the role of muscle contraction in bronchial obstruction.

Material and Methods. Preparation of Antigen: Crystalline egg albumin‡ was labelled with carrier free I^{131}, a radioactive isotope of iodine, by the method previously described for gamma globulin, with a single modification: 40 mc. of I^{131} was used for each 100 mg. of albumin instead of the 20 mc. of I^{131} used for 100 mg. of globulin. The increased I^{131} was necessary because under the conditions of our labelling procedure, the albumin combined with somewhat less than ½ as much of the available I^{131} as did the globulin. (This difference may well be because of the lower tyrosine content of the albumin.) The albumin so labelled showed the same chemical stability as the labelled globulin.

Experimental Procedure: The minimum lethal shock dose of albumin was between 0.25 and 0.5 mg., not sufficient to carry a traceable amount of radioactivity. It was necessary to use 4 mg. of labelled albumin as the shock dose in order to have measurable activity levels in the tissues. In so doing, we exceeded the minimum lethal dose by a factor of approximately 10, and thereby probably lost some contrast in tissue antigen concentration values and in autoradiographs because of excess antigen in the blood.

Animals. Twenty-nine male guinea pigs weighing between 250 gm. and 300 gm. were used. Sensitizing injections in all instances consisted of 25 mg. of protein given intraperitoneally. All shock injections were made into the left femoral vein. The radioactive al-

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‡ Crystalline egg albumin was furnished by the Physical Chemistry Department of Harvard Medical School.

bumin was given as a 10% aqueous solution.

Eleven guinea pigs to be used as non-sensitized controls were given intravenous injections of 4 mg. of radioactive albumin; 6 were killed 2 minutes after injection, and 5 were killed 4 minutes after injection.

Ten guinea pigs were given a sensitizing injection of non-radioactive iodinated albumin prepared as previously described without the addition of I^{131}. After a 2 week sensitization period, a shock dose of 4 mg. of radioactive albumin was given intravenously. Typical anaphylactic shock ensued and terminated fatally in from 1½ to 2½ minutes in all animals.

Eight guinea pigs were sensitized to bovine fibrinogen*. Two weeks later they were given an intravenous shock dose of 10 mg. of bovine fibrinogen and a simultaneous intravenous injection of 4 mg. of radioactive albumin. Typical anaphylactic shock ensued and terminated fatally in from 2 to 2½ minutes in all animals. In this group of animals the labelled albumin was subjected to all the physiologic effects of shock without being the specific shock producing antigen.

Detailed postmortem studies were made on all these animals in order to locate the radioactive antigen in the tissues, and to observe histologic changes concerned with bronchial obstruction in the shocked animals.

As previously described, determinations of the Geiger count were made on all tissues and organs to ascertain the concentration of radioactivity. Those tissues containing significant activity (lungs, livers, and kidneys) were autoradiographed so that the distribution of radioactivity could be observed histologically.

The Geiger count was also determined for the whole blood of all animals and for the plasma and cellular fractions of blood after centrifuging. Using blood activity concentrations and the formula given by Flexner, Gellhorn and Merrell[1] to determine the blood volume from body weight, we calculated the per cent of the injected labelled antigen which was still in the blood at time of death (see Table).

Observations. Anaphylactic shock caused by either albumin or fibrinogen was classic, beginning with respiratory difficulty about 15 seconds after injection and terminating fatally within 1½ to 2½ minutes after injection.

AUTOPSY RADIOACTIVITY DETERMINATIONS. Samples of all the various tissues of these experimental animals were examined; only the blood, lungs, liver, and kidneys showed measurable activity. Two minutes after injection the activity concentration of the blood in all animals was higher than that of any other tissue. The plasma fraction contained virtually all the radioactivity found in the blood; the cellular elements contained only insignificant traces.

Because there was some variation both in the weights of the animals and in the rate of loss of activity from the blood of the different groups, and

TABLE 1.—TISSUE ACTIVITY DETERMINATIONS
(Mean values & standard errors)

	No. of animals	*% original injected activity in total blood volume at death*	*Activity per gm. of tissue expressed as per cent of activity per gm. of blood*		
			Lung	*Liver*	*Kidney*
Non Sensitized Controls—2 minutes	6	73.5 ± 1.6	44.7 ± 2.8	63.3 ± 2.2	62.7 ± 7.4
Non Sensitized Controls—4 minutes	5	52.0 ± 5.8	insufficient activity	162.4 ± 25.0	not determined
Albumin Shock	10	78.3 ± 4.2	67.9 ± 5.7	49.3 ± 6	28.0 ± 0.4 (4 determinations only)
Fibrinogen Shock (albumin tracer)	8	89.1 ± 3.8	43.8 ± 1.9	58.4 ± 9.1	25.1 ± 4.6

* Bovine fibrinogen was generously supplied by Armour and Company, Chemical Research and Development Department, Chicago, Illinois.

because part of the activity found in any tissue was dependent upon the activity in the blood retained in that tissue, it was believed that the most accurate measurement of activity concentration in the tissues would be expressed as: $\frac{\text{activity/gm. of tissue}}{\text{activity/gm. of blood}} \times 100$, *i. e.*, tissue activity as per cent of blood activity for each animal. No attempt at perfusion of the organs was made because the additional variable seemed undesirable. The activity concentration values calculated are summarized for each group in the accompanying Table.

Non-sensitized Controls. After intravenous injection of control animals, the labelled albumin rapidly escaped from the blood stream; 73.5% remained after 2 minutes and 52% remained after 4 minutes. The only tissues showing significant activity were lung, liver, and kidney. Two minutes after injection, the activity concentration of liver and kidney was 63% of that for blood, while the concentration of lung was 45%. Four minutes after injection, the activity concentration of the liver had nearly doubled, and it now had 162% of the activity concentration of the blood. This latter figure was in part due to the lowering of blood activity level. The lung activity was so low that accurate determinations were not possible. The drop in activity of the lung was roughly of the magnitude of the loss in activity of the blood. Determinations of the activity of the kidney were not made at 4 minutes.

Albumin Shocked Animals. At time of death 1½ to 2½ minutes after injection, the blood of the animals shocked with albumin contained approximately the same amount of activity as the 2 minute control group. Seventy-eight per cent of the injected activity was found in the blood. The activity content of the lung was 68% of that of the blood, about 1½ times that found in the control lungs. The activity value of the liver was somewhat lower than the control value. In the 4 instances measured, the activity values of the kidney were only 28% of the activity values of the blood, markedly lower than in the controls.

Fibrinogen Shocked Animals. Two to 2½ minutes after animals were injected with fibrinogen, they died in anaphylaxis indistinguishable from that caused by albumin. However, in these animals the radioactive albumin had a definitely different distribution than in those in which albumin was the shocking antigen. The loss of activity from the blood was definitely slower than in either of the above groups. Eighty-nine per cent of the injected activity was still in the blood 2 minutes after injection. The activity concentration of the lung was 44% of that of the blood and approximately the same as the control value. The activity value of the liver was 58%, again almost the same as in the controls, but the activity value of the kidney was 25%, near that found in the albumin shocked group and less than ½ the control value.

AUTORADIOGRAPHS AND MORPHOLOGIC OBSERVATIONS. *Non-sensitized Controls.* The lungs collapsed when the thorax was opened. On microscopic observation the lungs seemed to be passively collapsed with partial closure of most of the alveoli and a variable degree of bronchial narrowing resulting from papillary infolding of bronchial mucosa. The bronchial wall was made up of an inconspicuous submucosa, a prominent but not obviously contracted layer of smooth muscle, external to which was a loose stroma of fibrous tissue containing cartilage plates, inconspicuous networks of lymphatics and blood vessels, and a few lymphocytes and histiocytes (Figs. 1 and 2).

Autoradiographs of the lungs showed activity only within blood vessels. The livers had a relatively diffuse scattering of activity with definite concentrations

only within the large blood vessels. This technique is not refined enough to permit distinction between activity contained within hepatic sinusoids and that contained in the cells of the cords. However, in the kidneys in addition to a diffuse generalized activity in the cortex, there was a definite concentration of activity in several of the collecting tubules of the medulla. These foci of increased activity corresponded to accumulations of eosinophilic, homogeneous, protein-like material seen within these tubules on histologic sections.

Albumin Shocked Animals. The lungs of these animals bulged forth when the thorax was opened. Histologic study of the pulmonary air passages and alveoli revealed distention distal to the small bronchi and constriction proximal to that point. In the walls of the small and medium sized bronchi there were 2 important observations. First, there was contraction of the bronchial smooth muscle as evidenced by increased thickness of the muscle layer and increased papillary infolding of bronchial mucosa with resulting almost complete occlusion of bronchial lumen. Second, in the loose collagenous tissue external to the smooth muscle of the bronchial wall and extending to the associated pulmonary artery, the blood and lymph vessels of the bronchial plexus

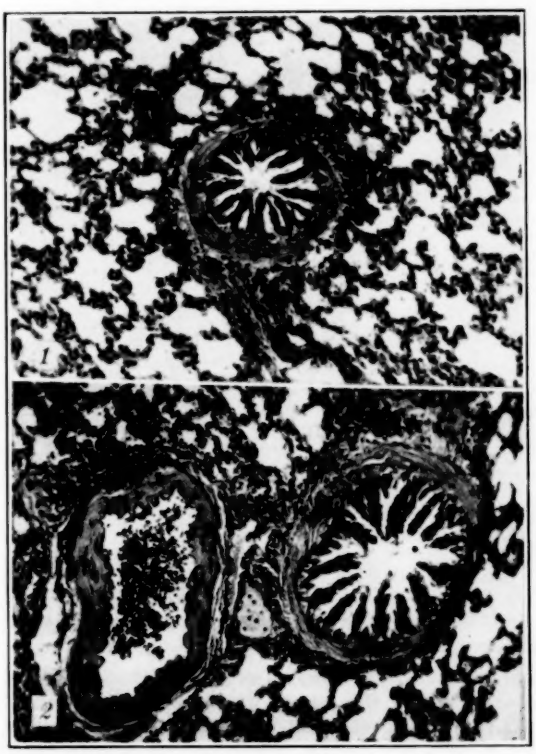

FIG. 1. Small bronchus of normal control lung. Note infolding of mucosa and prominent smooth muscle layer. The vessels in the bronchial wall are inconspicuous (X 130).

FIG. 2. Medium bronchus of normal control lung. Mucosal infolding and smooth muscle are similar to those in small bronchus. The tissue between bronchus and associated pulmonary artery is inconspicuous and contains a collapsed lymphatic vessel (X 130).

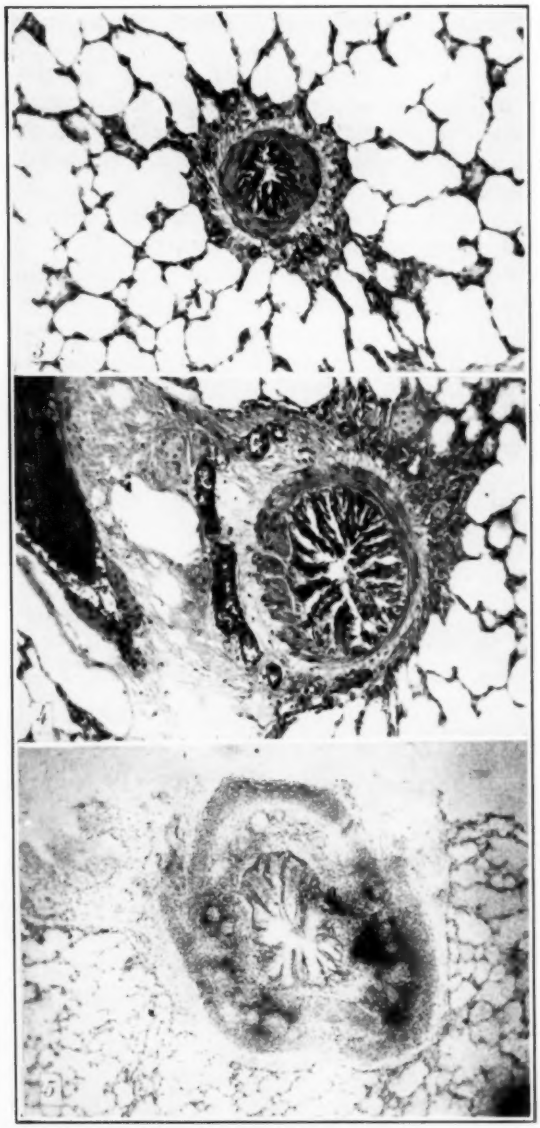

FIG. 3. Small bronchus of albumin shocked animal. (Compare with Fig. 1.) The lumen is virtually occluded by close packed folds of mucosa resulting apparently from smooth muscle contraction. There is a moderate amount of interstitial edema in the wall of the bronchus outside the muscle layer. In this edematous tissue several dilated capillaries are visible. The alveoli are distended in contrast to the partially collapsed alveoli in the control lung (X 130).

FIG. 4. Medium bronchus of albumin shocked animal. (Compare with Fig. 2.) The lumen is filled with folds of mucosa and the smooth muscle appears in part contracted. There is much interstitial edema in the bronchial wall and loose collagenous tissue between bronchus and pulmonary artery at left. The blood vessels and lymphatics are markedly distended (X 130).

FIG. 5. Autoradiograph of a large bronchus of albumin shocked animal. The black granular silver deposits indicate radioactive albumin within the tissue section. The activity is most evident in the collagenous tissue of the bronchial wall between the smooth muscle layer and the cartilage rings. Dilated vessels are also discernible in this zone (X 50).

were markedly dilated, and there was considerable interstitial edema in this region (Figs. 3 and 4).

Autoradiographs showed a significant concentration of radioactivity in the edematous tissue within the bronchial wall and adventitia of associated pulmonary artery (Fig. 5). This activity localization was not as clearly defined as that in the autoradiographs of globulin shocked lungs.

Fibrinogen Shocked Animals. Gross and histologic study of the lungs revealed changes identical with those seen in the albumin shocked animals. The autoradiographs, however, showed little or none of the concentration of activity in the edematous bronchial walls that was seen in the animals shocked with albumin.

The observations made on liver and kidney were similar to those made on the group shocked with albumin.

Discussion. On the basis of the observations in this study of anaphylactic shock, it is postulated that the most exact determinations on the localization of antigens labelled with radioactive elements will be secured if the antigen is of large molecular size and if the shocking dose of the antigen is given in the minimally effective amount. The larger the protein molecule, the less will be the non-specific diffusibility and the greater the definition of antigen localization. The minimum effective doses will insure that the greatest possible proportion of the labelled antigen will be acted upon by the sensitized tissues and that no unbound antigen will be present in the blood and tissues to obscure localization.

Several of the observations on the distribution of egg albumin in the various groups of animals are of interest, especially in the light of the findings previously obtained with labelled gamma globulin. In discussing the present findings, it will be necessary to make numerous references to and comparisons with the material reported earlier.

The rate of loss of egg albumin from the blood stream of non-sensitized animals was more than 3 times as rapid as the rate of globulin. (In 2 minutes 26.5% and in 4 minutes 48% of the albumin had disappeared from the blood, while in from 5 to 8 minutes only 15% of globulin had disappeared.) The apparent explanation for at least a large part of this rapid loss of albumin was renal excretion (which did not occur with globulin), as evidenced by urine high in activity found in the renal collecting tubules 2 minutes after injection. The kidneys of animals given radioactive albumin had a high activity concentration, while those given globulin had a very low activity concentration.

Apparently albumin with a molecular weight of 33,800 passes the renal barrier, while globulin with a molecular weight of approximately 150,000 does not. These findings of rapid renal excretion of egg albumin agree well with those of Kenton[2], who measured albumin loss from circulation in rabbits and guinea pigs using a serum reaction technique. He found that after intravenous injections of egg albumin into rabbits, 85% of the albumin had disappeared from the blood within 1 hour.

It is worthy of note that with our procedure, in as little as 2 minutes after injection the albumin had already gone at least as far as the collecting tubules in the renal pyramids. Kenton reported the presence of albumin in the bladder urine of rabbits in less than 10 minutes after intravenous injection.

The difference in rate of loss of albumin from the blood stream under the 3 conditions of this experiment is interesting. Albumin was lost at about the same rate in non-sensitized animals and in animals in which albumin was the specific shock producing antigen,

while it was lost approximately ½ as rapidly during shock when it was not the specific shock producing antigen, but only present as a non-specific protein tracer substance. A possible explanation for this difference is suggested by the data of this experiment. There appear to be 3 factors influencing loss of albumin from the circulation: first, renal excretion; second, non-specific phagocytosis best seen in the liver of non-sensitized animals and non-specific leakage from the vascular system; and third, fixation of specific antigen by sensitized tissues in shock, most marked in the lungs, but probably present to some degree in other tissues. The first 2 factors account for much of the albumin loss from the blood in non-sensitized animals. In shock produced by albumin the third factor would operate, but because of circulatory difficulties in anaphylaxis, the first 2 factors would be less effective. These changes apparently nearly balance each other since the total albumin loss from the blood is about the same in specific shock and in non-sensitized animals. In shock produced by fibrinogen where albumin is not the shock producing antigen, none of the 3 factors is maximum, and albumin is lost from the circulation less rapidly than in the other 2 conditions.

Analysis of the lung activity values for the 3 groups of animals sheds some light on the nature of the antigen concentration in the lungs during shock. The activity concentrations of the lungs of control animals and animals shocked with fibrinogen are approximately equal, while the values for lungs of animals shocked with albumin are 50% greater than either. Thus, when albumin was the shocking antigen, it was found in increased amounts in the lungs, but when it was present in the blood stream during shock without being the specific antigen, it was not concentrated in the lungs. If it can be assumed that the physiologic mechanisms of albumin and fibrinogen induced anaphylaxis are similar, our observations indicate that the increased uptake of specific antigen by the lungs in shock results at least in part from a specific fixation of the shocking antigen.

The findings of high renal activity concentration in control kidneys with activity in the collecting tubules, in contrast to low activity values in both albumin and fibrinogen shock, suggest that the low values in shock do not depend on the specificity of albumin as the shocking protein, but rather result from the altered physiologic mechanisms in anaphylaxis. Presumably this is caused by reduced blood pressure or selective renal ischemia which interferes with glomerular filtration of the albumin.

Histologic study of the lungs in rapidly fatal shock suggested a somewhat different mechanism of bronchial obstruction than in more prolonged globulin shock. In the globulin shock which lasted from 5 to 8 minutes there was evidence of a transitory bronchial smooth muscle contraction in the first few minutes of shock which had disappeared by the time of death. There was at time of death, however, a marked interstitial edema within the wall of the bronchus which appeared to maintain bronchial rigidity and obstruction. This edema began to form early in shock and increased progressively until death. The albumin shock terminated fatally in about 2 minutes. At time of death there was evidence of an irregular contraction of bronchial smooth muscle causing bronchial stenosis most marked in the medium sized bronchi. The edema of the bronchial wall was of moderate degree. The contraction of bronchial smooth muscle in the albumin shocked lungs was more marked but in general corresponded to that seen in inter-

mediate stages of globulin shock 2 to 3 minutes after antigen injection.

Thus, it appears that bronchial smooth muscle contraction in anaphylaxis occurs early in shock and then subsides; if death occurs in this early stage, the muscle contraction predominates in the picture of bronchial obstruction. If, however, the shock is more prolonged, the smooth muscle relaxes, and the edema in the bronchial walls which increases during shock becomes the most important factor in bronchial obstruction.

Conclusions. 1. In anaphylactic shock in the guinea pig induced by egg albumin there is edema formation and a concentration of antigen in the bronchial fibrous tissue similar to that previously reported for bovine gamma globulin.

2. This antigen localization seems to be a binding of specific antigen at the site of one of the sensitivity reactions, the bronchial wall.

3. The bronchial stenosis present at time of death in albumin induced anaphylactic shock is caused primarily by smooth muscle contraction present about some of the bronchi, and to a lesser degree of moderate edema formation in the collagenous connective tissue about most of the bronchi.

4. Egg albumin is rapidly lost from the blood stream. Part of this loss is caused by renal excretion.

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REACTION OF TISSUES TO ADMINISTRATION OF A PYROGENIC PREPARATION FROM A PSEUDOMONAS SPECIES*

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Artificial production of an increase in body temperature is a relatively new addition to modern therapeutics. It is now generally held that spontaneous fever may be a benign effort on the part of nature to combat disease. Rozenblem of Odessa in 1876 treated psychotics by inoculation with the spirochaete of relapsing fever but it was not until 1918 that Wagner-Jauregg popularized artificial fever therapy by reporting success in treating neurosyphilitics with induced malaria[7]. Since that time other methods have been utilized to produce artificial fever in attempts to treat a large number of diseases.

Methods of inducing therapeutic fevers may be classed under the headings, physical and chemical. There are some basic differences in the physiological responses of the body to physically induced fevers. From the practical standpoint, induction of fever by physical means is the more difficult, requires expensive equipment and careful supervision by trained personnel, thus limiting the availability of such therapy. By chemically induced fever is meant the elevation of body temperature by administration, usually intravenously, of one of a number of foreign materials such as foreign proteins, extracts of bacterial cells or killed organisms themselves. In this category should also be placed the fever of infectious diseases. Furthermore, a non-toxic derivative of the euglobulin fraction of inflammatory exudates, "pyrexin", has been reported by Menkin[8] to produce a fever in animals when injected intravenously.

Tui[12] and his colleagues have studied the chemical nature of pyrogens obtained from a number of bacteria and reported separation of a purified pyrogen from a stock suspension of the killed organism, *E. typhosa*. Morgan[9], and Rodney and Welcke[11] have added information which leads to the belief that the bacterial pyrogens may be complex carbohydrates rather than proteins.

At the present time typhoid and para-typhoid vaccines are agents commonly used to induce therapeutic fever chemically. The pyrogenic factor is only one of a number of products of

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the bacterial cell and other factors may be responsible for some of the toxic symptoms that accompany their administration. Development of tolerance to repeated injections of such pyrogenic mixtures is marked, with the result that large increases in the dose are required in the courses of treatment.

Ginger and his colleagues[5] have been engaged for some time in purification and chemical identification of a pyrogenic factor obtained from a Pseudomonas species (Type culture No. 9229), selected because it is not commonly pathogenic and can be cultured easily. The purified material, known as Pyromen, is highly pyrogenic in small doses and apparently has little toxicity. The material does not give any of the usual tests for protein but does contain approximately 6% nitrogen which has been shown to be primarily attributable to the nucleic acid present. The active factor appears to be a complex polysaccharide and contains hexosamine as the only reducing sugar. Pyromen forms a stable colloidal dispersion in physiological saline solution which is satisfactory for parenteral administration.

Experimental studies with Pyromen are in progress in this and other laboratories. Minimum pyrogenic doses* were found to be in the range of 0.05 gamma to 10.0 gamma per kg. of body weight, depending upon what animal species was used. Pyrogenic and vascular responses were obtained with as little as 0.05 gamma of Pyromen per kg. in human subjects. The order of sensitivity of animals, from greatest to least, was found to be as follows: dog, rabbit, cat, monkey, guinea pig, and rat. Retching, vomiting, urination and defecation sometimes occurred in dogs and cats after doses as low as 25 gamma per kg., but these animals tolerated doses as high as 5000 gamma per kg. without other toxic symptoms. In rabbits toxic symptoms, including loss of righting reflexes and marked increases in heart rate and respiration, manifested themselves only with more massive doses. The monkey showed no toxic symptoms with doses of approximately 3000 gamma per kg. The minimum lethal dose was not accurately determined (see Table 1).

In view of the possibility that this purified pyrogen from a Pseudomonas species would have advantages over other pyrogenic substances commonly employed in fever therapy, it was thought desirable to study its effect over prolonged periods and in massive dosages upon various tissues and organs of experimental animals before extending its use clinically. We were especially interested in learning whether it induced marked pathological change in vital organs.

Material and Methods. Table 1 summarizes the experiments with this new pyrogen and with a similarly prepared extract of *E. typhosa*. Only those animals from which extensive series of tissues were prepared histologically have been tabulated. These consisted of 10 rabbits and 1 monkey (dose given intravenously) and 9 guinea pigs and 1 rat (intraperitoneally). Each administration to rabbits and the monkey produced a febrile response. The average peak for both Pyromen and the extract of *E. typhosa* was approximately 1.7° F., with no significant difference between the two. The highest individual response was 3.6° F.; the lowest was 0.6° F. The average duration of fever was 4 hours. Records of changes in body temperature were incomplete for the other animals. Control animals received pyrogen-free saline solutions and exhibited no symptoms of infectious diseases during their residence in the laboratory colony.

At the conclusion of experiments the animals were anesthetized with Nembutal. Most of them were then killed by instituting a perfusion-fixation technique employing a gum acacia saline solution followed immediately by 10%

* The minimum pyrogenic dose, as defined by Tui[12], was approximately 1.0 gamma per kg. of body weight of the rabbit.

formalin in a gum acacia saline solution. This method[6] of killing and fixing the tissues assured preservation within 5 to 8 minutes of all of them except the heart, into which the cannula for the perfusion was inserted. In a few animals small pieces of tissue were fixed by immersion in 10% formalin. Sample pieces of most tissues and organs were removed and placed in separate vials of fixing fluid after the perfusion. Tissues from control animals were preserved in similar manners. The stains used were hematoxylin and eosin for all except the central nervous system which was prepared by a buffered thionin technique.

Detailed histological studies were not carried out on all tissues and organs. When preliminary examination of the sections clearly revealed no difference between experimental and control animals, a number of them were disregarded and attention was concentrated on the brain, kidneys, liver, suprarenal glands, lymph nodes, bone marrow and spleen. All slides were studied by the pathologist (W.A.R.) without his knowledge of the identity of experimental and control specimens.

Results and Comment. Significant histological changes were limited to the kidneys, lymph nodes, bone marrow, and spleen. Most other organs

TABLE 1. SUMMARY OF EXPERIMENTS IN RESPECT TO SUBSTANCES TESTED DOSAGES USED AND DURATION.

Animal		Substance Tested	Duration of Experiment (days)	Number of Doses	Total Dosage (gamma)
Rab.	7	Pyromen	19	5	556
Rab.	6	"	27	5	556
Rab.	122	"	295	13	622
Rab.	69	"	159	17	3,121
Rab.	120	"	303	17	4,484
Rab.	106	"	280	22	24,117
Rab.	29	"	218	12	68,400*
Rab.	40	"	101	5	200,940†
Rab.	11	Typhoid	19	5	425
Rab.	8	"	27	5	617
Rab.	78	Control			
Rab.	1	"			
Rab.	2	"			
Monk.	1	Pyromen	72	5	482
G. Pig	3	"	6	3	49
G. Pig	4	"	6	3	149
G. Pig	1	"	7	1	348
G. Pig	16	"	17	5	375
G. Pig	2	"	1	1	385
G. Pig	7	"	4	1	394
G. Pig	9	Typhoid	1	1	415
G. Pig	10	"	7	1	435
G. Pig	8	"	4	1	450
G. Pig	13	Control			
Rat	4	Pyromen	1	1	18,000‡

* Four doses totaling 66,800 gamma, given over a 2½ hour period on the final day, produced toxic symptoms but failed to kill the animal.

† A final dose of 200,000 gamma was followed by death in 1 hour and 49 minutes, small hemorrhages were found in Peyer's Patches.

‡ A single dose killed the animal in 3¼ hours. Hemorrhages were observed in the intestines, liver and lymph nodes. Another rat (No. 3) received a single dose of 18,000 gamma of Pyromen but showed no toxic symptoms and no pathological changes grossly.

appeared to be unaffected. The livers of some of the animals exhibited small areas of leukocytic infiltration, minute foci of necrosis or minute granuloma formations. There was no significant difference in the livers of the animals receiving Pyromen from those receiving the extract of *E. typhosa* and those of the control animals. Therefore the liver changes may be assumed to have been unrelated to the administration of the drugs.

The change in the rabbit and guinea pig kidneys was principally in the nature of cloudy swelling in the distal convoluted tubules. This was observed inconstantly and it varied considerably. One of the control rabbits (No. 1) showed as marked changes as one of the experimental rabbits (No. 7). Fever was slight in the one monkey and its kidneys appeared to be normal. It is possible that some of the tubular changes observed in the other animals were related to the febrile response rather than to the drugs.

The suprarenal glands of the rabbits that had received recent dosages of Pyromen showed changes which were most marked in the zona reticularis. Cells were swollen, full of droplets and even vacuolated, and the zone was thicker than in the controls. The glands of rabbits receiving the most prolonged massive dosages were of relatively normal appearance, but contained clumps of swollen cells in the reticularis. The picture suggested acceleration of cortical secretory activity.†

The most consistent alterations were observed in the spleens, lymph nodes and bone marrow of the rabbits. Macrophages, reticulo-endothelial cells and lymphocytes were present in unusually great numbers. The spleen showed marked increase in amount of pigment in the phagocytes, larger numbers of lymphocytes in the red pulp than usual, reduction in the amount of blood in the sinusoids and appearance of centers of extra-medullary granulocytic hemopoiesis in the pulp cords. The bone marrow displayed an apparent hypercellularity, especially in the number of myelocytes and phagocytic reticulum cells. The lymph nodes often had large germinal centers.* In other words, the lymphoid and myeloid organs were interpreted as showing varying degrees of hyperactivity, hyperplasia and sometimes metaplasia. It was noted that the most marked changes occurred in the animals receiving the most prolonged and massive doses of Pyromen, but even those receiving smaller amounts of this drug over shorter periods of time showed increased phagocytosis of the products of blood corpuscle destruction. The control animals and those receiving treatment with the typhoid extract failed to show the changes in question, but only 2 animals received prolonged treatment with the extract of *E. typhosa*. In view of Doan's[1] report that physically induced fever resulted in a large increase in phagocytic cells in lymph nodes, spleen and liver, the present failure to observe changes after giving the extract of *E. typhosa* may lack significance.

Changes in myeloid and lymphoid organs of the guinea pigs that received several doses of Pyromen were like those in the rabbits. The splenic corpuscles, lymph nodules and lymph nodes of the 1 monkey had large germinal centers. Sections of the spleen of 2 untreated monkeys showed no indication of hyperactivity in the lymphatic centers.

† In a new series of experiments since this article was written, adrenal cortical hypertrophy and hyperactivity have been demonstrated during administration of frequent small doses of a similar pyrogenic extract. Results will be reported in a future article.

* In rabbits receiving greatest dosages, degenerated centers were observed in some nodes and granules that appeared to be fragments of nuclei were numerous.

Other investigators have reported histological changes induced by administration of pyrogenic substances. Commonly, there are alterations in proportions of white blood corpuscles. For example, granulocytic leukocytosis followed the use of a pyrogenic extract of *E. typhosa,* according to Favorite and Morgan[3]. The present investigators have encountered early leukopenia followed by leukocytosis, with a shift to the left, in the dog and man after administration of Pyromen.

Pathological changes after administering an extract of *E. typhosa* were observed in heart muscle, lung, liver, spleen, bone marrow, lymphatic tissue, suprarenal glands, intestines and the peripheral blood vessels by Favorite and Morgan[2], and Morgan[10]. The purified extract of a Pseudomonas species, Pyromen, used in the present experiments in rabbits, guinea pigs and 1 monkey had no such deleterious effects in the doses administered. Toxic doses of the Shear polysaccharide from *S. marcescens* have been reported to induce marked congestion and hemorrhages in dogs and guinea pigs[4]. Only in the 1 rat of the present series were such changes encountered with Pyromen, and that animal received a lethal dose.

Summary. The administration of massive doses of a purified extract of a Pseudomonas species and the repeated administration of the drug to 7 rabbits, 8 guinea pigs and 1 monkey induced no striking pathological changes. A variable, although never great, amount of cloudy swelling was encountered in the kidneys.

Histological changes in the suprarenal glands, lymphoid and myeloid organs were encountered in all animals receiving this extract but were not observed in those receiving pyrogen-free saline solution. The principal changes were: increased production of macrophages and lymphocytes in all species studied, and initiation of production of myelocytes and granulocytes in the spleens of rabbits receiving prolonged treatments. The suprarenal cortex appeared to have undergone some hypertrophy.

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INFARCTION OF APPENDICES EPIPLOICAE*

WITH A REPORT OF THREE CASES AND A BRIEF REVIEW OF THE LITERATURE

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During the past 13 months we have encountered 3 patients in whom disease of the epiploic appendages has produced acute symptoms necessitating laparotomy. Though rare, disorders of these structures occur with sufficient frequency to demand their consideration in the differential diagnosis of intra-abdominal conditions. It is felt that more familiarity with the anatomy of these appendages and the clinical manifestations of their disorders will bring to light a higher incidence than a perusal of the literature would indicate. Hence, the addition of 3 more cases to the literature is thought to be worthwhile.

Anatomy and Functions of the Appendices Epiploicae. The description of these organs in most standard textbooks is relegated to a few lines in the footnotes on the pages relating to the colon. It is even more surprising to note that their presence is not even indicated in some of the anatomical drawings in these texts. The epiploic appendages are flattened projections of serosa-enclosed fat arranged in a longitudinal manner along the colon. Although there is great variability in their arrangement, there is a tendency for them to be located in 2 rows, one on the medial side of the anterior taenia coli and one on the lateral side of the posterolateral taenia. The altered position of the taenia in the transverse colon likewise alters the position of the epiploic appendages. However, this arrangement is by no means constant, 1 or 3 rows being frequently seen. They may vary in size from a few millimeters up to 15 cm. in length; they may be tubular, conical, multilobulated, saccular, or leaf-shaped. They may be attached to the wall of the bowel by broad bases or by narrow pedicles. The average adult has about 100 of these appendages and their combined weight is generally about one-fourth that of the omentum, which gives some credence to the belief that they are fat depots. As a general rule they are more conspicuous in obese persons, particularly those who have recently lost weight, indicating that they may be among the last of the fat stores to be utilized by the body. They tend to be more numerous on the transverse, descending, and particularly on the sigmoid colon. They are not found on the rectum. Pines *et al.*[14] made a painstaking study of the vascular supply of the colon and the epiploic appendages.

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They injected the vessels with a mixture of red lead and starch in order to trace the smaller branches to their terminations in channels of the intestinal wall. They noted that these vessels do not enter the wall directly at the mesenteric border as do the vasa recti of the small intestine, but that they divide at the mesenteric border of the colon within the peritoneal fat and then encircle the wall of the bowel subperitoneally, giving off small branches to the wall. The injections also indicated that these vessels carry along with them a layer of protective subserous fat in the mesentery. The main vessels were found to continue into the fat of the epiploic appendages where they generally describe inverted U-shaped arcades from which branches run into the intestinal wall proximally and into the epiploic fat distally. Their conclusion was that the epiploic appendages are merely protective fat pockets for the redundant intestinal vessels when the intestinal wall is collapsed. They felt that this protective mechanism of vascular redundancy is necessary to prevent compression of the vessels and obliteration of their lumens when the bowel is distended.

Most investigators are in agreement that the epiploic appendages serve as protective agents and act as barriers against injury in the same manner as does the omentum. Support is lent to this postulation by the frequency with which they are found adherent to areas which are the seats of inflammatory reactions. Patterson has suggested that they may act as protective external colonic pads cushioning the colon with its semi-solid contents. Other investigators feel that the epiploic appendages are entirely functionless.

PATHOLOGICAL CONSIDERATIONS. Among the morbid conditions to which the epiploic appendages may fall heir are torsion; thrombosis of the vessels; infarction; cystic, hyaline, or calcareous degeneration; simple necrosis; gangrene; inflammation; adhesions, hyperplasia; and secondary carcinomatous implantations. Torsion is responsible for the vast majority of clinical syndromes. The cause of torsion of the appendices epiploicae remains obscure and is subject to controversy. It would seem that twisting on a mechanical basis might occur in obese patients having abnormally long appendages with narrow pedicles. However, Pines and his co-workers[14] found that torsion may occur with equal frequency in appendages with short wide pedicles. Pines quotes Payr who postulates that, since the epiploic appendiceal veins are longer than the corresponding arteries, the former become twisted around the latter with the production of infarction on the basis of venous occlusion. Klingenstein[8] cites 2 cases in which it was rather conclusively proved that torsion of the epiploic appendages was a result of other inflammatory lesions of the abdominal cavity. Torsion of the appendages within hernial sacs may be explained as a result of a twist imparted to the structure in its passage through an internal inguinal or femoral ring. Torsion and thrombosis with subsequent gangrene may result in the formation of a fibrous tissue mass, and this ultimately may become detached from the remaining normal tissue and cast off into the peritoneal cavity as a foreign body. Such foreign bodies have been termed *Corpora aliena adiposa*. Virchow, in 1863, called attention to their relationship to the epiploic appendages.

An appendix epiploica may be the primary seat of inflammation as the result of a diverticulum forming directly into its base. Inflammation by direct extension from adjoining organs is common.

Giffin *et al.*[4] in 1941 reviewed the literature and were able to collect 49 cases in which symptomatic primary lesions of epiploic appendages were responsible for abdominal symptoms requiring operations. To this total he added 10 instances encountered at the Mayo Clinic between 1919 and April, 1941. In addition cases have since been reported by Upham and McGrattan[17], Moore[12], LeVay[9], Milroy[11], Harte[5], Porter[15], Byberg and Lam[2], Simpson[16], Ives[6], Kirkham and Zerlin[7], and Marbury and Jackson[10]. Three of Moore's patients, Harte's case, and one of Giffin's cannot be included in any study of the symptomatology produced by diseased epiploic appendage because there were secondary effects such as bowel obstruction and incarceration of an epiploic appendage within a hernial sac which produced a clinical syndrome completely obscuring the symptoms produced by the diseased epiploic appendage *per se*. However, with our 3 cases, there remain a total of 82 cases for consideration.

Analysis of Signs and Symptoms. The pre-operative diagnoses made in these 82 cases are shown in Table 1. From this it may be seen that accurate appendicitis is by far the most common with diverticulitis being the next most frequent. The single case in which the correct diagnosis was made pre-operatively is credited to Babcock[5].

TABLE 1. PRE-OPERATIVE DIAGNOSES IN 82 CASES OF DISORDERS OF EPIPLOIC APPENDAGES

Appendicitis	39
Diverticulitis	9
Torsion of Ovarian Cyst	4
Appendicitis and Cholecystitis	2
Torsion of an Epiploic Appendage	1
All Others	27

The site of pain was most common in the right lower quadrant of the abdomen, with the lower left quadrant next in order of frequency. In a few cases the pain was first felt in the epigastrium with later migration to the lower right or left quadrant; however, this is exceptional. The location of pain in the entire series is shown in Table 2.

TABLE 2. LOCATION OF PAIN IN DISORDERS OF EPIPLOIC APPENDAGE

Lower Right Quadrant	39
Lower Left Quadrant	28
Epigastrium	6
Lower Portion of Abdomen	4
Generalized	4
Right Upper Quadrant	2
Rectum	1

Other signs and symptoms encountered are shown in Table 3.

TABLE 3. OTHER SIGNS AND SYMPTOMS OF DISORDERS OF EPIPLOIC APPENDAGES

Nausea alone	10
Nausea and vomiting	38
Tenderness alone	28
Tenderness and Rigidity	65
Palpable Mass	14
Fever (over 99.4)	13
Leukocytosis (over 10,000)	19

Seventy one patients had acute symptoms at the time of operation, while 11 had chronic symptoms. The lesions found at operation are shown in Table 4. It is probable that the diagnosis of torsion in many of these cases was made by inference, since the usual pathologic finding is hemorrhagic infarction.

TABLE 4. FINDINGS AT OPERATION IN 82 CASES OF DISORDERS OF EPIPLOIC APPENDAGES

Torsion of Epiploic Appendages	58
Infarction of Epiploic Appendages	16
Inflammation of Epiploic Appendages	7
Gangrene of Epiploic Appendages	1

Giffin in considering obesity as a factor in the genesis of the diseased

tags, found that the ratio of obese patients to those of normal or less than normal weight was nearly 2 to 1, considering 150 pounds as the arbitrary borderline when all of the Mayo Clinic cases were considered.

Case Reports. Case No. 1—C. E. M., No. 36707, a 22-year old white male, was admitted to the Indianapolis Veterans Administration Hospital on June 23, 1947, because of abdominal pain. The pain had started 36 hours previously in the right lower quadrant and was accompanied by nausea but no vomiting. He stated that the pain subsided, allowing a comfortable night's rest but that it had recurred upon arising in the morning. He was seen by his local family physician who had prescribed ice packs but the patient had experienced no relief from this procedure.

Physical examination revealed a moderately obese, young, white male weighing 180 pounds and measuring 67 inches in height. Positive findings were limited to the abdomen where moderate point tenderness was found in the right lower quadrant. There was no rigidity. No masses were palpable. Rectal examination was negative. There were 10,200 leukocytes; polymorphonuclears 65%; lymphocytes 53%; and monocytes 2%. The urine showed: specific gravity 1.015; reaction, alkaline; albumin negative; sugar negative; microscopic: occasional white blood cells. His temperature was 98.8° F.

The patient was kept under observation and on the following day (June 24), there was essentially no change in signs and symptoms. The leukocyte count was 7,100 with 74% polymorphonuclear leukocytes and 26% lymphocytes. A blood smear for lead stippling was negative. The temperature was 99.6° F.

A diagnosis of appendicitis, acute, subsiding was made and laparotomy was performed.

The appendix showed no evidence of acute inflammation grossly. However, a small epiploic fat pad measuring about 1 to 1½ cm. in its greatest diameter was seen on the lateral aspect of the terminal cecum. This epiploic fat tab was dark in color and attached by a narrow pedicle which was acutely injected. Microscopically, the epiploic appendage revealed diffuse hemorrhage and foci of polymorphonuclear leukocytic infiltration, together with edema and early necrosis. A slight fibrinopurulent exudate was noted on the surface. Sections through the vermiform appendix revealed no evidence of inflammation. Diagnosis: Hemorrhagic infarct of appendix epiploica.

Case No. 2. O. R. R., No. 40193, A 38 year old white male physician, entered the Veterans Hospital on Jan. 30, 1948, because of abdominal pain of 20 hours' duration. He had been well until about 3 p. m. of the preceding afternoon when he noted the appearance of right lower quadrant pain and distress, unaccompanied by any other symptoms. He had no nausea or vomiting. The patient had never experienced a similar previous attack. Previous illness included malaria in 1943 and 1944, atypical pneumonia in 1943, and peptic ulcer in 1946, adequately controlled by medical therapy.

Physical examination revealed a rather obese, white male weighing 170 pounds and measuring 66½ inches in height. Positive findings were essentially limited to the abdomen where point tenderness, rebound tenderness, and mild rigidity were noted in the right lower quadrant. Rectal examination was negative. The leukocyte count was 15,000 with 63% polymorphonuclears, 29% lymphocytes, 6% monocytes, and 2% eosinophils. The urine showed: specific gravity 1.018; reaction, acid; albumen, trace; sugar, negative; microscopic: occasional granular casts. The temperature was 98.6° F. orally. A presumptive diagnosis of acute appendicitis was made and the patient was subjected to laparotomy.

The vermiform appendix was found to show no gross evidence of inflammation. However, an intensely hemorrhagic appendix epiploica was found on the anterolateral aspect of the cecum. It measured about 2 cm. in its greatest dimension. Attached to it by a narrow pedicle was a much smaller tab of fat which showed no pathological changes. The serosa covering the hemorrhagic lobule was dull. On microscopic section were seen considerable hemorrhage and inflammatory changes in and about the blood vessels. Some of the vessels revealed thrombosis and beginning disintegration of the tissue forming their walls. A fibrinous exudate was present on the surface. Sections through the vermiform appendix revealed a normal mucosa and muscularis. However, a slight fibrinous exudate was present on the serosa and scattered inflammatory cells were found distributed in the subserosa. The pathologist's diagnosis was (1) hemorrhagic infarction of appendix epiploica; (2) periappendicitis, secondary to (1).

Case No. 3. W. H. W., No. 41916, a 37 year old colored male, was admitted to the Indianapolis Veterans Administration Hospital on July 13, 1948, because of discomfort in the right lower quadrant of the abdomen of 24 hours' duration. He had experienced no nausea or vomiting.

Physical examination revealed a robust, somewhat obese, middle-aged colored male weighing 180 pounds and measuring 66 inches in height. The abdomen was markedly but rather diffusely tender in the right lower quadrant. Fairly well developed muscle spasm was present. Tenderness was noted on digital examination of the rectum. The leukocyte count was 17,500, with polymorphonuclears 72%; lymphocytes 27%; and monocytes 1%. The urine showed: specific gravity 1.022; reaction, acid; albumin, negative; sugar, negative; microscopic, negative; temperature 99.2°.

A diagnosis of acute appendicitis was made and a laparotomy performed shortly after admission. When the peritoneum was incised a small amount of cloudy fluid was noted in the region of the cecum. On the lateral wall of the cecum was an inflammatory mass presenting a firm irregular, shelving surface sloping to blend with the normal wall of the cecum. At the shelving portion the lesion was raised about 1 cm. above the surrounding surface, and the lesion measured about 3.5 cm. in length and about 2.5 cm. in width. The vermiform appendix was found to be grossly normal. Normal tissue was noted to exist between the base of the appendix and the lesion described. A routine appendectomy was carried out with inversion of the stump through a purse string suture. Two biopsy specimens were removed from the granulomatous lesion. The terminal ilium was examined for a distance of about 3 feet, as well as the mesentery. No lymphadenopathy was found. All other parts of the bowel appeared normal. Closure was accomplished and the patient returned to his room in good condition. His post-operative convalescence was uneventful.

Microscopically the biopsy specimens were seen to consist of fatty tissue in which there were considerable inflammatory changes. Fibrin and edema fluid were widely scattered through various fatty lobules and hemorrhage was also present. In addition there was some infiltration by polymorphonuclear leukocytes and phagocytes. A fairly thick fibrinopurulent exudate was seen on the surface in some places. Occasionally the fatty tissue appeared to be somewhat devitalized. The pathological diagnosis was "Hemorrhage and inflammation of pericecal fatty tissue, probably appendix epiploica."

Comment. Torsion of the pedicles of epiploic appendages has been established as the cause of acute abdominal symptoms in the cases reported in this paper. As is well known by most surgeons and pathologists, many patients operated upon for appendicitis are found to have normal vermiform appendices, and in a not inconsiderable number of such patients no cause is established for the clinical syndrome necessitating laparotomy. It is suggested that torsion or other acute changes in the epiploic appendages may be the offending factor in some of these instances. Laparotomy may not elucidate the diagnosis unless careful exploration is performed to eliminate this possibility. Fortunately, it is probably not necessary to explore the entire colon because the local pain, tenderness, and muscle spasm are usually present in the portion of the abdomen in which the diseased epiploic appendage is located. It is realized that torsion with subsequent necrosis and detachment is entirely compatible with the patient's future well-being in spite of the temporary morbidity. A survey of the literature does not indicate that serious complications are frequent, and it is probable that conservative treatment without operation would probably be adequate in most cases, if the diagnosis could be established clinically. The typical picture caused by acute torsion consists of moderate localized pain and tenderness in the abdomen, not usually preceded by nausea, vomiting, or epigastric cramps. The absence of these latter findings is important in differentiating this syndrome from that of acute appendicitis. The patient is usually an adult with a tendency toward obesity. Significant fever and leukocytosis are absent in the majority of cases, and when the total leukocyte count is increased, the differential count is usually not abnormal. An awareness of this condition and a thorough search for diseased epiploic

appendages, particularly in that not inconsiderable percentage of cases where no other pathological process is found to account for the symptoms, should result in more frequent diagnosis of this condition in the future.

Summary. 1. Three instances of infarction of epiploic appendages are described.

2. The clinical and laboratory findings are reviewed.

3. Certain anatomical and physiological features of these structures are pointed out.

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THE PRESENT STATUS OF PENICILLIN IN THE TREATMENT OF SYPHILIS IN PREGNANCY AND INFANTILE CONGENITAL SYPHILIS

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THE information on penicillin therapy in the prevention and treatment of congenital syphilis, first discussed by Lentz, Ingraham, Beerman and Stokes[21] in 1944, has crystallized sufficiently since then to make possible a rather definite formulation of principles. This statement, prepared initially for presentation before the World Health Organization Expert Committee on Venereal Infections*, brings up to date previously published material[17] and supplies a review of the current literature which has served to substantiate, supplement and clarify the original clinical observations.

During the years 1941 through 1948 there has been a 24.3% decrease in cases of congenital syphilis in continental United States reported to the Public Health Service, but with information still being received at the rate of 11,407 new cases during the first 9 months of 1949[4], it is evident that this medical and public health problem is one which still needs attention. Heyman and McCain's[15] recent detailed analysis of the factors responsible for congenital syphi-

* Washington, D. C.—Oct. 10-20, 1949.

lis in 77 infants serves to substantiate the fact that in the prevention of this disease, as with other communicable diseases, effective treatment is not the only factor in its control. Most prominent among the circumstances contributing to congenital syphilis are failure to recognize the fresh infection as it develops in late pregnancy and delay on the part of the expectant mother in reporting for medical supervision to the extent that effective prenatal care is impossible. About one-third of the syphilitic infants resulted in the report just mentioned when mothers, seronegative and clinically normal at the time of the first prenatal visit, were found to be seropositive at the time of delivery. Three-fourths of the mothers who gave birth to syphilitic infants had received no treatment prior to conception. In only 1 instance in 32 in which treatment was given during pregnancy was it begun before the fifth month and one-fourth first reported for medical care at the time of delivery. The importance of a variety of factors which affect the incidence of congenital syphilis is accordingly self apparent, and treatment alone, no matter how effective in itself, cannot completely control this type of syphilis without attention to the other contributing causes which are largely in the fields of public health education and socio-economics.

One important collateral development in the studies of the effectiveness of penicillin in the prevention of congenital syphilis has been the realization of the need of a more critical evaluation of results of metal chemotherapy. At least 3 types of clinical control have become recognized as desirable or essential. These are: 1, some knowledge of the expected outcome of non-syphilitic pregnancies; 2, information with respect to the effect of untreated syphilis in pregnancy; 3, critical study of the value of arsenic and bismuth treatment of the pregnant woman, in material comparable to that in which the result of penicillin therapy is being tried. Several authors have delved into one or another aspect of this problem with result that some of the essential information has been supplied as follows.

When a non-syphilitic control group is included the occurrence of unfavorable outcome of pregnancy is apparently less among the adequately treated syphilitic women than it is among the so called normal (or non-syphilitic) controls. The probable explanation for this is that early syphilis, which is most likely to be transmitted to the fetus, occurs with greatest frequency among young and otherwise healthy women, so that, if the infection can be arrested or cured, the chance of giving birth to a normal infant is slightly better than the average group which includes all ages and complications of pregnancy. The comparison of the effects of age and race specific series with some consideration, if necessary, of the number of primiparas or cases of toxemia or dystocia in the particular series would probably largely do away with these differences. Cole and his coworkers[5], for example, found that among 414 mothers with syphilis treated during pregnancy, the infant fatality rate was 51.6 per 1000 live births, which compared very favorably to the 1944 stillbirth rate for New York City, from which the greater portion of the material was drawn, of 80.9 per 1000. Wammock *et al.*[30], reporting from Philadelphia General Hospital, found 12.4% unsatisfactory outcome among the non-syphilitic control group in comparison to from 6 to 7% unsatisfactory outcome in the adequately treated syphilitic group of pregnant women.

Information as to the effect of untreated syphilis on the fetus is much more difficult to obtain from the cur-

rent literature although there are many references to this subject in the older writings. The importance of the subject is mentioned by Curtis[7] while Wammock *et al.* give the following information from the 1945 to 1948 Philadelphia General Hospital material: Untreated pregnant women with open lesions of early syphilis give birth to dead or diseased infants in approximately 100% of cases. Untreated women with symptomless syphilis of less than 4 years duration may give birth to normal infants in as high as 30% of cases. Women with syphilis of long standing rarely give birth to diseased infants even if untreated. In this group the expectancy of a normal living infant for a pregnant woman with late syphilis was, again, better than the expectancy for the control group. The real risk of infection of the fetus, accordingly, arises among women with untreated recently acquired syphilis.

The value of very small amounts of spirillicidal drugs, either before or during pregnancy, in the prevention of congenital syphilis has been very prominently emphasized by analyses concerned with the third type of clinical control[2,10]. In an analysis of 341 cases, almost all treated with arsenic and bismuth, Barnett and Read found only 10 infants proved conclusively to have syphilis and "these were born of mothers who had no treatment or very little treatment and in all but one of whom the infection at the time of delivery was either definitely or probably early." These authors found further that in no case in which therapy was given prior to conception was infection transmitted to the child. The interesting suggestion is also made by Barnett and Read that much of the information contained in the older medical literature on the high incidence of congenital syphilis is largely negated by the inadequacy of diagnosis employed in both mother and infant. In particular are mentioned the tendency to attribute all fetal deaths in syphilitic mothers to syphilis, often without adequate study or controls and the placing of too much reliance on positive serologic tests in living infant offspring of seropositive mothers during the first few weeks of life. In good current practice almost all of these infants, seropositive at birth, prove on subsequent medical follow up not to have syphilis.

Both Barnett and Read, and Goodwin and Farber, basing their analyses on results of metal chemotherapy, differ seriously with the dictum to treat with each pregnancy and feel that adequately treated maternal syphilis of long standing entails very little risk to the fetus. Heyman and McCain[15] wisely point out that, from the practical standpoint, the interpretation of what constitutes "adequate" therapy depends not so much upon the amount of treatment as upon the course of the disease after treatment. This is often difficult to determine, requires considerable data which are not always readily available, and a great deal of experience in its interpretation.

Most authors who have studied the question are in agreement that there is one situation in which arsenical-bismuth treatment is rather ineffectual in controlling infection of the fetus. That is in recently acquired syphilis when treatment is delaved until the last weeks of pregnancy. In such instances the fetus is usually infected prior to the commencement of treatment and a syphilitic infant is the rule. Special mention is made of this point because it is becoming increasingly apparent that one of the special virtues of penicillin is in controlling this situation (Cf. 15% failures after intensive arsenotherapy of syphilitic pregnant women[7]). With this much background

to assist in its interpretation, we now present a statement of principles with respect to the use of penicillin in the prevention of congenital syphilis.

Pregnancy and Syphilis. The following facts seem *reasonably well established in the treatment of the syphilitic pregnant woman with penicillin:*

1. PENICILLIN READILY PERMEATES THE HUMAN PLACENTA. This occurs in the later months of the pregnancy[13,16,32] and indeed as early as the tenth week of gestation[31]. It has been shown experimentally through determination of penicillin in fetal tissues and through healing of syphilitic lesions in newborn infants following antepartum therapy[6,29]. It has also been demonstrated in animals[12].

2. VERY SMALL AMOUNTS OF PENICILLIN, even total dosage in the magnitude of 300,000 to 600,000 Oxford units of penicillin given to women with active recently acquired syphilis in the latter months of pregnancy, *are often sufficient to prevent infection of the fetus in utero*, and to result in the birth of a healthy infant[5,17].

As corollaries: *A*, Even though a mother is not cured of her syphilis she may give birth to a normal infant through penicillin treatment during pregnancy[3,17].

B, Mothers with positive blood serologic tests for syphilis may give birth to normal healthy infants[1,18]. The frequency of this occurrence depends upon the clinical material, but may be considerable (in the magnitude of 80 to 90%), since the length of time following therapy even in those mothers in whom the response is ultimately favorable is often too short to expect reversal of the blood serologic test for syphilis from positive to complete negativity, during pregnancy.

C, The normal healthy infant may frequently have a positive blood serologic test for syphilis at birth following penicillin therapy of the mother. This again is because of the short length of time which frequently intervenes between treatment of the expectant mother and the delivery of the newborn child. The frequency of this occurrence depends upon the characteristics of the case material but may exceed 40% positive blood tests for syphilis in normal infant offspring of syphilitic mothers. (In Allen and Delp's report[1] 37 of 45 non-syphilitic infants were seropositive at birth.) Two recent observations are of interest and possibly of importance in interpreting the serologic test in early infancy. Cole *et al.*[5] found that there were no syphilitic infants among the penicillin treated mothers who were seronegative at delivery. They found also that all seropositive non-syphilitic infants were born of mothers treated after the fifth month of gestation. Tucker[29] observed several infants whose blood serologic test remained positive for abnormally long periods after birth (90 to 120 days) even though active syphilis was not demonstrated. It is thought that these may be syphilitic infants in whom treatment in utero was sufficient to cure the disease. If such is the case it would be anticipated that in some instances persistently positive titers in infants untreated postnatally might last even longer (4 to 6 months or more). This situation was not encountered or at least not recognized in syphilitic women treated prenatally with metal chemotherapy.

3. LARGER DOSES OF PENICILLIN. Pregnant women treated with larger amounts of penicillin will give birth to almost 100% non-syphilitic infants regardless of the stage of syphilis treated. The infrequent failures following penicillin treatment usually have resulted from one of two causes:

A, The fetus may have been diseased beyond any real hope of recovery be-

fore penicillin treatment is instituted. This occurs when active infection in the expectant mother is discovered only in the later weeks of the pregnancy (usually after the 32nd week of gestation). Under such circumstances the fetus living at the commencement of penicillin treatment may die suddenly during the course of therapy (placental shock, fetal Jarisch-Herxheimer reaction) or shortly thereafter and will be stillborn, sometimes macerated within a few days or weeks after treatment[3,6,15]. Living syphilitic infants have also been born sometimes prematurely, immediately following penicillin therapy[16].

B, A single course of penicillin treatment given to the expectant mother with active infectious syphilis, usually early in the pregnancy, may be insufficient to result in cure of the mother[15]. Under these circumstances the blood serologic test may show a high sustained reagin titer, or an initially favorable response may be followed by an increasing titer, at times with the development of infectious skin or mucous membrane lesions at or near the termination of the pregnancy. In such instances infection of the fetus will probably have occurred very late in the pregnancy. The newborn infant will usually be healthy appearing, though with positive blood serologic test, and detectable clinical signs of the disease will frequently not occur until he is 2 to 3 months of age or even slightly older.

4. Penicillin Need not be Supplemented by Arsenic or Bismuth. The results with penicillin alone are so good in protecting the fetus, between 97 and 100% satisfactory, that they cannot be expected to be improved by the addition of arsenicals or the heavy metals. The toxicity of arsenic, moreover, makes its use contraindicated in this circumstance when penicillin is more effective.

5. Treatment Reactions to Penicillin. *These have not* proved to be serious and do not normally necessitate any modification of the treatment course. The fear that penicillin may produce contraction of the uterus, placental separation or premature labor have proved to be groundless except in the case of the grossly diseased fetus discussed above. In general, it is considered best to give the mother and fetus the benefit of full treatment and to feel that in the occasional case when fetal death or miscarriage results during penicillin treatment, the infant could have been saved by *no* known means. All authors are in accord as to the value of penicillin in the prevention of congenital syphilis and there is uniform agreement that it is the treatment of choice in all stages of syphilis complicating pregnancy[5,6,7,11,17,18,25,29,30].

The following points are *still open to some controversy* or *discussion in the penicillin treatment of the syphilitic pregnant woman:*

1. The Optimum Treatment Course. Using aqueous penicillin in hospitalized patients, in giving individual injections every 2 to 3 hours of 40,000 to 50,000 Oxford units each, maximum protection of the fetus seems to be afforded by total penicillin dosage of 2.4 million units or more[18]. Cole *et al.*[5] found 8.9% syphilitic infants born to syphilitic mothers treated with less than 2.4 million units of penicillin and 2.5% syphilitic infants when the dosage was 2.4 million units or more. There is some reason to feel that this may not be optimum dosage for the "cure" of the maternal syphilis, and that larger amounts of penicillin for the mother may be required even though not necessary to protect the fetus. Since larger amounts of penicillin will not apparently harm the fetus, it seems best to gauge the dosage for the mother on the re-

quirements of the maternal syphilis rather than to base it on the optimum dosage to protect the fetus. The optimum *duration of the treatment* course with penicillin for the syphilitic pregnant woman likewise has not been finally determined. Studies till now have been concerned almost exclusively with treatment courses covering periods of 7 to 12 days. No adequate appraisal has been made of shorter treatment courses.

It is customary, provided there is no clinical or serologic evidence of activity of infection, to rely upon a single course of penicillin given during the pregnancy. The earlier this is given the better, since it is preferable to prevent infection of the fetus if possible. One of the advantages of penicillin therapy, however, is its ability to treat and cure fetal syphilis in utero, to the extent that surprisingly good results have been obtained even when treatment is delayed until very late in the pregnancy. In the Johns Hopkins material[29], for example, in which not a single living syphilitic infant resulted, 73.4% of the mothers were treated after the fifth month and 23% were treated after the seventh month; in the group reported by Cole[5] 43 (10%) of his patients were treated in the last month of pregnancy (average 23 days prior to delivery); in the University of Pennsylvania[18] material 25% of the aqueous penicillin series and 19% of the series treated with penicillin in absorption delaying vehicle were started after the 32nd week. Syphilitic infants born of mothers with active syphilis who have been treated with penicillin during pregnancy have averaged about 2%.

Since a significant proportion of mothers treated for syphilis during their pregnancy (possibly 20%) are not cured of this disease, medical follow-up of the mother postnatally is important irrespective of syphilis status of the newborn infant.

2. The Addition of Absorption Delaying Vehicles to Penicillin for Ambulatory Treatment. Because of the wide variety of circumstances attendant on the management of the syphilitic pregnant woman, not all of which admit hospital care and frequent injections of penicillin, a method of ambulatory treatment is a requisite. Initial studies of treating the syphilitic pregnant woman with the poorly standardized penicillin in oil beeswax preparations at first available gave results definitely inferior in the prevention of fetal infection to those obtained with aqueous penicillin treatment by frequent injection[18]. Currently available carefully standardized preparations of procaine penicillin G in absorption delaying vehicle with or without the use of 2% aluminum monostearate in which prolonged blood levels are assured seem to give satisfactory results when individual doses of 600,000 units of penicillin are given once daily, but the number of investigators reporting thus far is too small to come to a final opinion. The duration of such treatment courses has been 8 to 10 days totalling 4.8 to 6.0 million units of penicillin (Cf. Allen and Delp[1]). Peabody and Webster[24] have used intermittent type of therapy with penicillin in absorption delaying vehicle but have confined its use to pregnant women with latent syphilis or to those who have been previously treated. No syphilitic infants resulted. Provided the preparation used can be depended upon to give sustained blood and tissue levels of penicillin in both mother and fetus there is no reason to feel penicillin in absorption delaying vehicles is not satisfactory for the treatment of the syphilitic pregnant woman.

3. Retreatment in Subsequent Pregnancies. Provided a woman is "cured" of her syphilis by penicillin treatment, has no clinical manifesta-

tions of the disease, has a negative blood serologic test, and has not been reinfected through subsequent exposure, it has been shown beyond reasonable doubt that she may safely go through subsequent pregnancies untreated without danger of infection of the fetus[17, 18,19,28]. The crux of the problem here is the criteria of cure of the previously treated syphilis which are to be used in the pregnant woman. This problem of test of cure obviously is much broader than the management of syphilis in pregnancy and is concerned with the overall problem of establishing a cure of syphilis following penicillin therapy of any infected individual. Nonetheless, several research groups using their best acumen as to clinical cure of syphilis have withheld treatment in the subsequent pregnancies and have had success in the delivery of non-syphilitic fetuses in approximately 99% of cases or a failure rate of only about 1%. In the Johns Hopkins[28] series, totalling 111 infants, 27.9% of the mothers were seropositive at delivery. In the two University of Pennsylvania[18] series, totalling 130 infants, 31.5 and 34.2% of the mothers were seropositive at delivery. It is Tucker's opinion that "amounts of penicillin in excess of 2.4 million units, to which the syphilitic pregnant or non-pregnant woman has responded satisfactorily, are sufficient to guarantee healthy offspring in subsequent pregnancies, provided that relapse or reinfection does not occur." Because of the problems, both theoretical and practical, of establishing clinical cure of syphilis, it is not certain that withholding treatment in subsequent pregnancies following penicillin can, as yet, be recommended as a routine practice, particularly if the expectant mother is seropositive.

Infantile Syphilis. The facts in the penicillin treatment of infantile syphilis are less clearly established than for other types of the disease because of limitation in available case material, but some points seem reasonably well established and at least form a basis for discussion or future investigation.

The basic literature on this subject in this country has been summarized by Ingraham[17]. Reports from the foreign literature are now beginning to appear and for the most part are confirmatory of our experience[9,20] except for some tendency to think that penicillin therapy should be supplemented by metal chemotherapy[8]. Hasbun and Rosselot[14] give an excellent summary of response of congenital osseous syphilis to penicillin. Scully and Yamazaki[27] describe a case of congenital syphilitic nephrosis successfully treated with penicillin.

The time to treat infantile syphilis is prenatally. If this were universally accomplished infantile syphilis would virtually cease to exist. Every mother not studied for syphilis during her pregnancy should be studied for this disease at the time of delivery or at the time she presents her infant for pediatric care. In the management of infantile syphilis there is no satisfactory substitute for a knowledge of the existence of maternal syphilis.

The offspring of syphilitic parentage should be uniformly studied for syphilis, regardless of clinical appearance of good health, by blood serologic tests, by roentgenogram of the long bones in selected cases, by darkfield examination if lesions are present, and spinal fluid studies, as indicated, over a period not less than 4 months. A 6 month medical follow-up is probably desirable, but there is little demonstrated need of study for prenatally acquired syphilis beyond this period provided observation in infancy has been adequate. Congenital syphilis discovered in the late stages uniformly results from

inadequately observed and improperly treated infantile syphilis.

In debilitated infants with prenatally acquired syphilis the mortality rate is high (about 10 to 20%) in spite of penicillin treatment. The Pennsylvania group experienced a mortality rate of 18% in infants observed under 3 months of age, a 10% mortality between the age of 3 and 6 months, but no deaths in older infants with syphilis up to two years[26]. Pardo and Tucker[23] report for the Johns Hopkins group a 6.9% mortality in infants under 3 years, but most of these deaths were probably in the small infants. Morgan had 9 deaths (15.5%) in 58 infants[22]. Best results are obtained if the infant is hospitalized, if great care is taken with respect to supportive pediatric care directed toward maintenance of proper fluid, salt and protein balance; to good nutrition and the correction of existing anemia. Parenteral fluids and blood transfusion may be necessary.

Therapeutic shock (Jarisch-Herxheimer reaction) will occur in ½ of the infants with congenital syphilis[23] and may be severe, occasionally resulting in very high temperatures (104° to 105°F), circulatory collapse, or convulsive seizures. Because of the frequent occurrence of pneumonia and other intercurrent infections it is usually regarded as desirable not to modify the penicillin dosage and not to wait for any type of preparatory treatment other than expert pediatric care described above.

Several authors[17] have stressed the fact that one of the important reasons for the superiority of penicillin over other types of therapy in the infant is that it will treat intercurrent pyogenic infections as well as syphilis. The most common cause of death in infantile congenital syphilis is bronchopneumonia and almost every debilitated infant will have some complicating infection. "The danger resulting from uncontrolled bronchopneumonia far outweighs that of possible Herxheimer reaction" (Morgan[22]). Enkvist[8] also stresses the value of penicillin in curing infections which endanger life in the debilitated syphilitic infant.

No optimum treatment course for infantile syphilis has been established but common practice is as follows: 1. Use aqueous penicillin by frequent injection in hospitalized cases. There is no reason to feel that penicillin in absorption delaying vehicle would not be satisfactory but it has not been sufficiently tried to be certain of the results. In selected cases it has proved to be satisfactory in individual once daily dosage of 100,000 to 300,000 units per injection. (Cf. Morgan[22]). One practical problem which has been encountered in the emaciated infant is that there are very small amounts of tissue in the buttocks or elsewhere in which to make the injection. When preparations containing oil are used local reaction and irregular absorption are more likely to occur than in older children or adults.

2. Treatment has usually been continued over a period of 15 days. This is arbitrary and is based upon the fact that we are dealing with a severe infection for which maximum treatment is desirable.

3. Total dose which seems to be effective is from 100,000 units to 400,000 per kg. of body weight. This is usually given in 120 individual injections 3 hours apart when the aqueous penicillin is employed. There is little evidence that total dosage above 100,000 units per kg. is necessary or that it produces any better results.

4. It is not thought necessary to use any adjunct metal chemotherapy or preparatory specific treatment when penicillin is employed (Cf. Enkvist[8] for divergent point of view).

Serologic and clinical results in surviving infants with above dosage is at least the equal and possibly superior to results obtained with acquired syphilis. It has been a matter for some comment that infectious relapse following penicillin treatment of small infants is almost never seen. It is about 1% or less[17]. Response of blood serologic tests is in direct ratio to the age at which treatment is commenced: the earlier the treatment the better the response. In surviving infants in whom penicillin treatment is commenced under the age of 3 months[17,26], the serologic reversal to negativity approaches 100%. In infants first treated between the ages of 6 months and 2 years an increasing number remain with positive blood serologic tests for syphilis in spite of otherwise normal and healthy appearance. In Morgan's group of 38 infants under the age of 1 year, all but 4 became seronegative in from 6 weeks to 11 months (average 5 months) following treatment. There was one case of serologic relapse. Insufficient numbers of older infants have been followed for periods long enough to determine the significance of persistently positive blood tests in terms of late congenital syphilis, but it is assumed that these delayed manifestations have probably been aborted by the penicillin therapy.

Penicillin has proved to be the most valuable remedy yet available for the prevention of congenital syphilis, or for treating infantile congenital syphilis if the infection is not aborted by prenatal treatment. In both types of infection the effectiveness so closely approaches 100% that it becomes evident the complete disappearance of congenital syphilis from now on depends quite largely upon public education and public health administration. Congenital syphilis can be eliminated if our present medical knowledge can be applied.

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OTO-RHINO-LARYNGOLOGY

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OTOLARYNGOLOGIC MANIFESTATIONS OF BLOOD DYSCRASIAS: A CLINICOPATHOLOGIC REVIEW

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SOME blood dyscrasias manifest early otolaryngologic signs and symptoms and the patient is therefore likely to seek the aid of an otolaryngologist first. Although each of the blood dyscrasias is an entity, yet certain basic changes in the blood recur frequently in various conditions. Anemia, leukopenia and thrombopenia are observed as primary and secondary changes in many disorders of the hemopoietic tissues, and whenever present are likely to produce the same signs and symptoms. Bleeding from the nose, gums and into the skin and mucous membranes of the mouth resulting from a reduced platelet count explains the hemorrhages of acute leukemia, aplastic anemia and idiopathic thrombopenic purpura. Similarly certain tissue changes may occur in more than one blood dyscrasia and may cause identical results. Tissue infiltration by leukemic cells is common to the various types of leukemia and may by pressure cause deafness or other local symptoms. It is important to realize the disease nonspecifity of such signs and symptoms and to relate them to basic changes in the blood rather than to any one clinical disorder. Also the manifestations of some blood disorders are protean and a number of benign and malignant disease conditions may be simulated closely. The lymphadenopathy of infectious mononucleosis may suggest Hodgkin's disease, lymphosarcoma, lymphatic leukemia and lymph nodes enlarged from sepsis; and when there is extensive involvement of the mouth and throat the possibility of Vincent's angina, diphtheria, streptococcus sore throat and agranulocytosis must be considered. It is apparent that it is only through the correlation of clinical and laboratory data that the otolaryngologist will arrive at an accurate diagnosis and be in a position to institute early and proper treatment[71,75,103].

ANEMIA. Pallor is the most striking symptom of anemia. Skin pallor does not necessarily denote anemia. It is interesting that a patient with normal coloration in the buccal and pharyngeal mucous membranes and conjunctivae will rarely be found to be anemic. Acute loss of blood reveals a waxy dead whiteness of the skin and in chronic hemorrhagic anemia there is a distinctly sallow color. In pernicious

anemia the lemon yellow pallor which results from a combination of pallor with a yellow tint is seen only when the condition is well advanced. The yellow tint of the skin and mucous membranes is due to the increased amount of bilirubin in the blood when the red blood count is low. In recent years it is not so common to observe patients with this lemon-yellow color due to the fact that patients consult a physician earlier in the course of the disease and thus receive immediate and adequate treatment. The grayish tint to the skin and mucous membranes sometimes seen in cases of leukemia is not characteristic of the disorder. In some of the hemolytic anemias, especially in patients who have received frequent blood transfusions, the yellowish color of the skin may gradually assume a brownish discoloration due to hemosiderosis and hemochromatosis. In various systemic diseases the pallor of the skin and mucous membranes may be characteristic, but it is not diagnostic. These diseases include nephritis, hypothyroidism, malignant diseases and others. Pernicious anemia and microcytic hypochromic anemia associated with glossitis and dysphagia require special mention.

Pernicious Anemia. Pernicious anemia is a deficiency disease due to a lack of specific substance necessary for the growth and development of the erythrocyte. Clinical recognition of pernicious anemia is facilitated by certain oral and other gastrointestinal symptoms which are frequently present. The characteristic sore tongue or glossitis may be its earliest symptom and may appear when there is little or no anemia. Recurrent attacks of sore tongue occur in about two-thirds of the cases of pernicious anemia. Although this is characteristic for this disease, it is not specific. It is observed in Plummer-Vinson syndrome, hypochromic anemia, sprue, pellagra, anemia of pregnancy, malnutrition associated with dysentery and anemia, intestinal stricture, and in patients with achlorhydria associated with other diseases. In some cases of pernicious anemia the glossitis is very sore and painful and "beefy" in appearance. Frequently inflammation involving the gums, buccal mucous membrane and throat is elicited by history or physical examination. Small vesicular elevations may appear on the margins or involve the whole dorsum of the tongue and break down into shallow painful ulcers. The superficial whitish ulcers may resemble those observed in apthous stomatitis. After a number of these attacks the epithelium of the tongue atrophies, the papillae disappear and the smooth, glazed tongue characteristic of pernicious anemia remains. There may be a partial loss of taste.

Atrophic tongue changes are of greater clinical significance than an abnormally coated tongue; the latter finding is practically never observed in a patient with pernicious anemia in a relapse. Atrophy of the lingual papillae is usually associated with a systemic disease. A smooth red tongue is often due to a nutritional deficiency. Atrophic tongue changes are observed in pellagra, pernicious anemia, sprue and iron deficiency anemias[82]. Atrophic glossitis forms a part of the Plummer-Vinson syndrome.

The diagnostic triad of sore tongue, achlorhydria and neurologic manifestations of numbness and tingling form the clinical picture of pernicious anemia. The diagnosis is confirmed by the hematologic studies which in an unusual case may require the additional aid of bone marrow examination. The latter examination should always be done before specific treatment is begun as treatment rapidly alters the characteristic bone marrow pattern of per-

nicious anemia. Liver extract and Vitamin B12, particularly the former, continue to be the treatment of choice. If treatment is maintained throughout the life of the patient, an excellent state of well being is afforded.

PLUMMER-VINSON SYNDROME[126,127]. This syndrome which appears to occur mostly, if not exclusively, in women, is characterized by hypochromic anemia with or without achlorhydria, dysphagia and chronic inflammatory and atrophic changes in the mouth, pharynx and upper end of the esophagus. A number of investigators believe that the syndrome brings with it a special liability to cancer in those structures.

Plummer in 1908 and again in 1912 discussed the subject of cardiospasm and diffuse dilatation of the esophagus without anatomic stenosis[105,106]. There is no mention of anemia being associated with this condition as originally described by Plummer, although Vinson, who summarized the cases under Plummer's direction, states that this complex of dysphagia without organic obstruction, anemia and enlargement of the spleen was first pointed out by Plummer. It may be that the information was entirely obtained from Plummer by personal communication[129]. At any rate in 1922 Vinson[128] reported 69 cases of this condition under the title of "Hysterical Dysphagia". Since this report the syndrome has frequently been referred to as Plummer-Vinson syndrome. Suzman[121] has called attention to the fact that this condition has been previously described by Kelly[56] and Paterson[99] in 1919 in England in 2 separate papers entitled "Spasm at the Entrance of the Oesophagus" and "A Clinical Type of Dysphagia". Spasm was stressed by Kelly because of the fact that on passage of the esophagoscope, the folds of the narrowed esophagus gave way without undue pressure, and treatment consisted of dilatation. Paterson[100] particularly stressed the tongue devoid of papilla, and changes in the mucosa and bands in various positions across the opening of the esophagus so that the opening was irregular, or an obliquely placed slit, and not always in the median line. Treatment in Vinson's cases consisted of dilatation, a liberal diet with arsenic and iron for the anemia, and reassurance. In 1926 Moersch and Conner[84] also reported 65 cases, all in women. Glossitis was seen occasionally. The mucous membranes of the mouth were atrophic and dry, but webs or other membranous obstructions were not noted in the upper end of the esophagus. Splenomegaly was recorded in 20 of the 65 cases. Achlorhydria was present in 8 cases out of 10 instances in which gastric analysis was performed. Paresthesia of the extremities was a feature in 5 cases. The treatment was the same as that suggested by Vinson but Moersch and Conner noted that in some cases the anemia preceded the dysphagia, an occurrence which was not in accord with Vinson's view that the anemia was due to an improper diet following dysphagia. In the years from 1929 to 1935 there was great interest in the chronic microcytic anemia associated with this syndrome which was discussed under many different aspects according as they presented themselves to each author[1,4,23,44,45,51,55,80,81,83,90,133,140]. All the authors described a type of anemia, commonly microcytic and hypochromic with achlorhydria. Bone marrow examination showed a normoblastic hyperplasia[65]. Some of these observers noted that an enlargement of the spleen, a sore mouth, atrophic tongue and dysphagia was occasionally present among their cases. Witts[139] pointed out the close correspondence between Plummer-Vinson syndrome and achlorhydric anemia.

He stated that chronic microcytic anemia is much more common in women than men. It is not due, in his opinion, to any of the common causes of secondary anemia such as hemorrhage or infection, but is probably an independent disease. Achlorhydria precedes the anemia and may remain after the anemia is cured. Hoover[50] ascribed the dysphagia to a mechanical obstruction of the upper portion of the esophagus. The glossitis was described as an atrophic tongue which does not differ from that described in connection with other diseases. The need for careful follow-up was emphasized.

The sequence of the anemia and dysphagia has not been established. Suzman stated his belief that the manifestation of the syndrome, except for the dysphagia, are indistinguishable from those of idiopathic hypochromic anemia and several other types of hypochromic anemia with or without achlorhydria. The dysphagia is merely a complication of an already well known form of anemia, and there does not appear to be sufficient reason to regard the Plummer-Vinson syndrome as a separate clinical entity.

In the 8 cases reported by Suzman[121], 2 had had gastroenterostomies and 1 died from mediastinitis following the passage of a filiform bougie. Autopsy revealed that the mucosa of the tongue and esophagus showed hyperkeratinization with areas of desquamation and degenerative atrophic changes in the underlying muscle. There was no evidence of inflammation. The finding of vitamin A in the liver ruled out a deficiency of this vitamin as being responsible for hyperkeratinization of the epithelium. The presence of areas of mucous membrane simulating leukoplakia and containing immature cells exhibiting mitoses was interesting with respect to the tendency to development of malignant disease. Auerbach's plexes revealed no abnormality. One other case developed carcinoma in the pharynx and tongue but not of the upper end of the esophagus. In this connection the experimental work of Cordray[17] on anemic mice is interesting. They were fed a diet consisting wholly of milk. The milk diet contained all the essential vitamins but was extremely low in iron. At the end of a 5½ month period, the rats were weak, definitely underweight and the fur was very coarse and thin. They were sacrificed. The outstanding pathological change noted was the hyperkeratinization of the epithelial lining of the esophagus with proliferation of the epithelial layer and more frequent mitotic figures. Many pathologists regard this combination as a precancerous lesion. Since the only possible etiologic agent is the secondary anemia, Cordray inferred that marked protracted secondary anemia is capable of producing precancerous lesions in the esophagus.

From his observations Suzman[121] excluded as possibilities for the cause of the obstruction such conditions as hysteria[87], spasm, inflammation of the nerve supply, involvement of the Auerbach plexus similar to achalasia of the cardia and syphilis. He stated his belief that the underlying cause is iron deficiency caused by some gastric abnormality. In McGee and Goodwin's patient[91] who died of hemorrhage, autopsy examination showed an area of the esophagus where the mucous and submucous layers were broken and denuded. Beneath the mucous membrane there was evidence of a mild inflammatory reaction. Kerman[58] reported 2 cases of Plummer-Vinson syndrome and showed that there is a connection between gastric disease and atrophic conditions of the esophagus. There was reason to believe that there

may have been dietary deficiencies in these cases. There was constriction and obstruction of the lumen of the esophagus on the basis of ulceration and healing with the formation of bands and adhesions. Both patients died and an autopsy was performed on 1 of the patients. Microscopic examination of the mucous membrane of the esophagus showed thinning of the epithelial layer, with ulceration. The lamina propria and submucosa were replaced by dense collagenous tissue or infiltrated with lymphocytes. There was destruction of the muscularis mucosa. In the muscularis there was moderate fibrosis. Esophagoscopy caused the mediastinitis and death of the second patient.

A number of investigators have emphasized that there is a close relation between the lesions which develop at the upper end of the esophagus in Plummer-Vinson syndrome and carcinoma in the same location[14,99,122]. Others point out that both conditions are frequent in women and that the sequence is too frequent to be a coincidence. Ahlbom[2,3] noted that 90% of patients with postcricoid carcinoma were women, of whom 90% had had either Plummer-Vinson syndrome or simple achlorhydric anemia. It is interesting to observe that the syndrome is more frequent in Sweden than in other countries. Vinson[129], who found no esophageal lesions in his cases, noted that the majority of patients whom he saw at the Mayo Clinic were of English or Scandinavian extraction. He states that he has never seen hysterical dysphagia in the Jewish race. On the other hand Laub[61] and others deny a special liability to cancer in this condition. Laub studied 235 cases of carcinoma of the esophagus and from the histories of these cases he concluded that there is no causal connection between it and Plummer-Vinson syndrome. The age distribution of the women with this disease in his series was between 15 and 50 years of age. The anemia appeared at 18 to 20 years of age. In the ages between 20 and 30 years the women often lost their teeth, and glossitis later completed the picture. A buccal leukoplakia was observed in some of the cases. In about 25% of the cases the spleen was enlarged and the nails were brittle and spoon shaped. Laub thought that there might be some relation between the Plummer-Vinson syndrome and glandular disturbances. A hereditary factor was suggested in a case reported by McGibbon[92].

In addition to the anemia and dysphagia, there develops chronic inflammatory and atrophic changes in the lips, the tongue and the buccal and pharyngeal mucous membranes as well as in the upper part of the esophagus, the entrance to which is narrowed. These membranes become dry and inelastic; the tongue smooth and glazed, the lips thinned, stiff and cracked at the corners. The face gradually takes on a characteristic appearance. Systematic studies of the blood chemistry, metabolic and structural changes in cases of Plummer-Vinson syndrome are practically non-existent. Many of the authors mention this syndrome as occurring during the menopause, and Vinson and others regard the dysphagia as hysterical in nature. Although patients with Plummer-Vinson syndrome often show lack of free hydrochloric acid in the gastric contents, many show no such deficiency. Achlorhydria cannot be regarded as an essential finding; also it is very often difficult to perform a gastric analysis when the dysphagia is severe. Gastroscopy during life has revealed a pale, gray atrophic mucosa[86].

On the other hand the association of achylia with chronic hypochromic anemia (simple anemia) caused Faber

to suggest that it might be a nosological entity[27]. The glossitis takes the form of atrophy of the lingual papillae. The tongue appears smooth and red and is painful, but the glossitis rarely approaches the intensity observed in pernicious anemia. The tongue may be shrunken in appearance, not differing much from the tongue observed in other severe hypochromic anemias.

The commonest complaints are pain and burning sensations when solid food passes behind the larynx. Such patients eat slowly and swallow only a little at a time; occasionally only liquids can be swallowed. There may be choking spells due to spasm. The difficulty in swallowing usually comes on gradually and may be so severe as to interfere with nutrition. Waldenstrom[130], who prefers the term "sideropenic dysphagia" to Plummer-Vinson syndrome, has found the condition to be the most common disease of the esophagus in Sweden, more than twice as common as carcinoma. Although anemia was not present in all of his cases, a low plasma iron (sideropenia) was a constant finding. The roentgenological changes seen in the esophagus in sideropenic (Plummer-Vinson's) dysphagia are very typical. The site of the lesion is usually in the upper part of the esophagus just below the cricoid cartilage or, quite exceptionally, still lower down, but never as low as the crossing of the aorta. In most cases except the very advanced and severe ones the changes are most clearly or exclusively seen on the lateral view. The most frequent finding consists of very thin defects in the opacity produced by the barium, circular folds of the esophageal walls or broader cuff-like stricture below the membrane and a bulb-like swelling of the hypopharynx during a certain phase of the deglutition caused by a stagnation of the swallow before the stricture. In most cases the wall of the esophagus is smooth and its lumen above and below the stricture is the same. In order to obtain reliable Roentgen pictures of the hypopharynx and upper part of the esophagus, it is absolutely necessary to use the special technique described by the author[130,131].

Intense iron treatment gives a complete cure in practically all cases. This includes cases of koilonychia (spoon-nails) with or without anemia, patients who have rhagades in the corners of the mouth and ulcers on the tongue and others with burnings and itchings in the vulva. It has been observed that the angular stomatitis and glossitis which may accompany the chronic microcytic anemia can be corrected by iron therapy, even in the face of a deficiency diet[21]. Waldenstrom[130] points out that the disease is in all probability a chronic iron deficiency state and the most common symptom is the microcytic hypochromic anemia. The lack of iron in the body does not affect the different organs in the same way. The iron deficiency syndrome may also be associated with early greying of the hair, wrinkling of the skin, fissures in the corners of the mouth (perlèche), atrophy of the tongue, and brittleness and flattening of the finger nails[6]. In other cases, however, there may be found achlorhydria with epithelial abnormalities but without anemia. The tendency of these patients to develop hysterical manifestations has been noted by Sturgis[120]. Although the immediate effects of iron therapy are usually gratifying, including a reduction of the difficulties in swallowing, there is always a tendency for these patients to relapse unless treatment is maintained over a long period of observation. Furthermore, it seems probable that curing Plummer-Vinson syndrome (sideropenia), which is supposed to be the immediate cause of the

dysphagia, may be an important prophylactic measure against cancer of the mouth and throat.

LEUKEMIA. Petechiae and spontaneous bleeding from the mucous membranes of the nose, mouth and upper respiratory tract are among the earliest symptoms of leukemia. In addition, large areas of ecchymosis, extensive ulceration and noma-like lesions occur in patients with acute leukemia and terminal stages of chronic leukemia. The ulceration results from leukemic infiltrations as well as hemorrhage and invasion of the mucous membranes by spirochetes and pyogenic organisms found in the mouth. The lesions caused by these organisms may result in necrosis and destruction of tissue, formation of pseudomembranes and fetid odor. At times such lesions may be mistaken for Ludwig's angina, diphtheria, agranulocytosis or scurvy. The oral manifestations of leukemia have been reviewed by a number of investigators[12,13,77]. Favreul and Landais[28], and Pollosson and Lebeuf[108] described the noma-like lesions in acute leukemia, which may appear on the buccal surface of the cheek. There is no point of predilection. Wentz, Anday and Orban[135] reviewed the oral manifestations in 149 cases of leukemia and observed that the lesions were frequent and more extensive in the acute cases as compared with the chronic forms. Histological examination of the gingiva in patients with chronic myeloid leukemia showed characteristic changes consisting of a dense accumulation of immature leukocytes in the gingival connective tissue. Some of the immature white blood cells exhibited mitotic activity. Other tissue changes observed in the epithelium, connective tissue and blood vessels of the oral cavity appeared to be coincidental and not a direct result of the leukemic process. They concluded that the histologic changes of the gingiva are specific in the acute, nonspecific in the chronic leukemias. In chronic lymphatic leukemia the histologic picture is also not specific. This is because the cells of the infitration resemble too much those of a non-specific chronic inflammation. Forkner[33], and others[96] believe that diffuse marked swelling of the mucous membranes, particularly of the gingivae associated with bleeding, ulceration and necrosis, is especially characteristic of acute monocytic leukemia. Forkner states that in acute monocytic leukemia diffuse swelling of the gingivae with a tendency for the teeth to become submerged in the gums is encountered in a large majority of cases; whereas in acute myeloid and acute lymphatic leukemia the oral lesions are nonspecific. Other investigators, including the author, do not agree that there exists any difference in the lesions of the mouth in the various types of leukemia. In association with these lesions of the mucous membranes there may be diffuse cellulitis which extends into the deeper tissues of the face.

Clinically, oral lesions in acute leukemia may be simulated by other diseases[78,89]. In most cases a diagnosis by local examination alone is impossible. Agranulocytosis, severe sepsis, scurvy, thrombocytopenic purpura, hemophilia, infectious mononucleosis or myelophthisic anemias may give rise to serious diagnostic difficulties, especially in the differentiations from acute leukopenic leukemia. Of the 9 patients with oral lesions reported by Maloney[78], 7 first visited the doctor or dentist because of bleeding from the gums, trench mouth or pain in the jaw. Not infrequently cases have been reported illustrating the disastrous results of tooth extraction. Klumpp and Evans[59] recorded 8 cases of monocytic leukemia, 5 of which were discovered following extraction of teeth.

Localized leukemic infiltration in the upper respiratory tract is often the initial and most striking manifestation of leukemia. Early recognition of the blood disorder will avoid extensive operative procedures which may result in fatal postoperative hemorrhage. Videbech[125a] reported 3 cases of fatal hemorrhages after tonsillectomy and adenoidectomy. The nature of the disease was recognized only at autopsy. Intense leukemic infiltrations, particularly around the blood vessels of the mucous membranes of the paranasal sinuses in cases of lymphatic leukemia, was reported by Menzel[32] in 1924. Leukemic involvement of the upper respiratory tract may suggest the commencement of a large number of conditions such as tonsillitis, quincy, diphtheria, Vincent's angina, agranulocytosis, typhoid fever, septicemia from any cause and purpura hemorrhagica. Leukemic involvement of the larynx and trachea may cause cough, dyspnea and even death by stenosis of the larynx caused by leukemic infiltration of the laryngeal mucosa. Seelenfreund[32] reviewed 40 cases of acute and chronic leukemia associated with leukemic infiltration of the upper respiratory tract. The larynx was most frequently involved by the leukemic process. The other sites of involvement included the epiglottis, subglottis, false vocal cords, true vocal cords and arytenoids. Leukemic changes in the upper respiratory tract were divided by Jaffé[54] into the inflammatory ulcerative group and the tumor-like group. The inflammatory and ulcerative changes in the upper respiratory tract in leukemia occur in association with similar lesions in the oral cavity or independently of such lesions. The changes usually begin in the tonsils, spreading to the pillars of the tonsils and may involve the back of the tongue, pharynx, epiglottis and even spread to the larynx and trachea. A thick greenish-white membrane may cover the tongue, soft palate, pillars and tonsils. This membrane, which comes off easily in some cases, reveals a gangrenous sloughing, foul smelling, dirty, grayish exudate with an irregular deep ulceration. These pathologic changes consist first of hemorrhagic extravasation, as a part of the generalized hemorrhagic diathesis. The hemorrhagic areas then become infected, gangrenous and ulcerated, because in leukemic states the defense reactions of the body are diminished. The inflammatory ulcerative lesions occur most frequently in acute leukemia and are uncommon in chronic leukemia. The finding of ulcerative and gangrenous changes in chronic leukemia is usually the first sign of a shifting from the chronic stage into the acute stage of the leukemia. The second type of change in the upper respiratory tract in leukemia consists of tumor-like infiltration of the tissues by leukemic cells. Many cases reveal the first changes in the tonsils. Usually the tonsil on one side starts swelling and often this swelling extends down to involve the pharynx and epiglottis. Leukemic infiltration in the larynx and in the trachea may produce severe respiratory complications. The infiltrated lesions are quite firm and histologically are composed of leukemic cells. In rare instances the leukemic changes occur in the uvula before other manifestations of leukemia are observed. Chronic lymphatic leukemia, especially the subleukemic type, according to Jaffé, is the most common type to involve the upper respiratory tract and causes the most extensive proliferations. This investigator emphasized that an unaccounted-for enlargement of the tonsils in an elderly person is always suggestive of leukemia. Brunner and Fischer[11] described the changes in the tonsils in leukemia

which they regard as early manifestations of the disease. Beinfield[8] reports a case of myeloid leukemia where the chief complaint was pronounced swelling of the left side of the face and neck for one week with increasing inability to talk and swallow. The lesions of the mouth and the swelling of the neck and face suggested a number of diagnoses including cellulitis of the face, lymphadenitis of the neck, suppurative parotitis, necrosis of the alveolar process of the left side of the maxilla, possibly osteomyelitis, Vincent's angina, malignant conditions of the maxilla, syphilis, tuberculosis, agranulocytosis, metal toxemia, septicemia, infectious mononucleosis and leukemia. Careful study of the blood and bone marrow revealed the underlying condition to be myeloid leukemia. The author stressed the important fact that many an obscure disorder is hidden behind a screen of leukemia, the oral lesions being merely a local manifestation of a systemic disorder.

Involvement of the tonsils is occasionally found in a condition related to leukemia but differing from typical leukemia by the distinctly malignant character of the infiltration, namely leukosarcoma (lymphosarcoma with a leukemic blood pattern). Lymphosarcoma of the tonsil at first is unilateral, but it becomes bilateral later; the cervical lymph nodes are usually enlarged. Carver[18] has called attention to the fact that lymphosarcoma is often overlooked. Any peculiar irregularity or firm rubbery part of a tonsil should be regarded with suspicion. Lymphosarcoma of the tonsil seldom ulcerates. It has been suggested that all tonsils that are removed from patients beyond the age of puberty be examined histologically. Sarcoma of the tonsil is not a common tumor. Whitcomb[137], who reviewed the literature and reported 7 cases, noted that it is not recognized early. Sarcoma of the tonsil should be distinguished from squamous cell carcinoma of the anterior faucial pillar, the commonest malignant tumor in the region of the tonsil. A large mass below the angle of the jaw is a common and conspicuous sign of sarcoma of the tonsil. Since sarcoma tissue may look like tonsil tissue, failure to note the malignant growth at biopsy has little meaning; repeated biopsies may be needed for a correct diagnosis.

Carcinoma is the most common malignant tumor of the larynx[19]. In approximately 80% of all cases, cancer of the larynx starts on the vocal cords, the first symptom being hoarseness. Leiomyosarcoma of the larynx is of rare occurrence. Only one case was found in the literature by Frank[36]. Approximately 1% of all malignant growths of the larynx are sarcomas, and leiomyosarcoma is exceedingly rare. Giant lymph follicle hyperplasia of the nasopharynx[101] has been reported as part of a generalized involvement of lymphoid tissue of the body. In the case reported the tumor mass arose from the nasopharynx and projected downward into the oropharynx. The generalized lymphadenopathy and splenomegaly were associated with a normal blood picture.

Primary plasma-cell tumors of the upper air passages and oral cavity[29,35,39,49,116,132] are rare compared with those arising in the bone marrow. They may occur in the nasal, pharyngeal, or oral mucous membranes as a solitary localized tumor or as a generalized process associated with multiple myeloma or plasma cell leukemia. In the upper respiratory tract the tumors appear as sessile or polypoid grayish-red swellings that tend to be somewhat lobulated as they increase in size. Some of the tumors may fill the greater part of the nasopharynx. They seldom ulcerate. The tumors are composed very largely

of plasma cells in massed formations supported by a reticular stroma of connective tissue. Usually the solitary lesions show normal blood, bone marrow and urine findings, and the Roentgen-ray examination of the bones are negative. When the masses are multiple the regional nodes are enlarged. The tumors cause no symptoms other than mechanical difficulties such as would be found with any comparable enlargement. Plasmacytomata may be mistaken for a lymphosarcoma, but are usually benign, although sometimes showing a tendency to invasion. Stout and Kenney[118] collected 104 cases in the literature with an analysis of treatment, complications and survival periods. They noted that the condition is 4 times as frequent in men as in women and that three-fourths of the cases developed in the fifth, sixth and seventh decades of life. They also discussed the principal sites of involvement, location of metastases, complications, treatment and survival periods.

Chloroma is a rare malignant disorder of the hemopoietic organs, closely related to leukemia. These tumors have a special predilection for the cranium. They characteristically invade the sinuses, orbits, lids, temporal bones and more rarely the oral and nasal cavities, but they are not confined to these regions. The condition produces very extensive infiltrations of the upper respiratory tract and the local process is quite destructive, much more so than the local lesions of myeloid and lymphatic leukemia. The blood picture is that of an atypical myeloblastic leukemia. In the cranial bones and their cavities the tumors are observed as solid or fluid masses, and frequently have a greenish tint. Levy and Loff[64] collected 162 cases in the literature and stressed the features of special interest to the otorhinologists. Chloroma may be mistaken for suppurative or malignant diseases of the ears and sinuses and useless operative procedures may be instituted if the condition is not previously recognized by a careful hematologic study.

The aural lesions observed clinically and on histologic examination usually constitute local manifestations of a generalized leukemic infiltration of the organs and tissues of the body. A variety of lesions have been described including hemorrhages, exudative processes and leukemic infiltrations of the external meatus, drum membrane, middle ear and external ear and their adnexa. The early literature on the ear in leukemia has been reviewed in part by Forkner[32], Fraser[37] and Love[77]. Vidal[125] in 1856 and Isambert[52] in 1860 reported deafness in cases of leukemia, and Gottstein[41] in 1880 was the first to present a clear clinical picture of Meniere's syndrome in cases of leukemia. Politzer[107] in 1885 for the first time correlated the clinical and histological findings in a case of leukemia at autopsy.

Hemorrhages which may combine with leukemic infiltrations are the main factors in the production of symptoms in leukemic involvement of the ear. The external ear is least frequently involved, but hemorrhages and ulcerations have been reported. In the middle ear hemorrhages combined with leukemic infiltrations and frequently complicated by infectious changes have been observed. Even the mucous membrane of the Eustachian tube may become involved in this process. The symptoms of otitis media due to leukemic involvement are characterized by deafness (conduction type) usually associated with tinnitus but without pain and vertigo. When hemorrhage takes place in the middle ear, the bulging drum (hemotympanum) takes on a bluish discoloration[43]. Jaffé[54] found an otitis media character-

ized by extensive destruction of bone in 10% of the cases of leukemia in which he was permitted to open the skull. The inner ear is the part most frequently involved by leukemic changes, and of these, hemorrhage plays a more important role than infiltration. So-called hemorrhagic fibrinous labyrinthitis is found most frequently in leukemic involvement of the inner ear. Jaffé stressed the fact that it is not so much a labyrinthitis as a hemorrhage into the perilymphatic spaces which causes a collapse of the endolymphatic spaces. The hematoma later becomes organized by granulation tissue, which in turn may be followed by leukemic infiltration. In other cases the granular tissue may become ossified, producing otitis interna ossificans and causing total ablation of function. Other changes that have been observed are hydrops of the endo-lymphatic spaces of the labyrinth with extreme distention and leukemic infiltration in the vestibular ganglion. The most marked symptoms of the leukemic ear occur with involvement of the inner ear. Small circumscribed hemorrhages into the labyrinth may be resorbed without producing any symptoms. Large and diffuse hemorrhage into the labyrinth produces the typical symptoms of Ménière's syndrome. The onset is sudden and all the symptoms are severe. Sudden deafness may be the first symptom of a leukemia[124]. Hemorrhagic involvement of both portions of the inner ear is characterized by deafness, tinnitus and violent vertigo. In cases of Ménière's syndrome due to leukemia, subsequent clinical examination reveals complete deafness and loss of vestibular response in the affected ear. If death occurs soon after the attack, histologic examination shows hemorrhage into the labyrinth. If the patient survives for a time after the Ménière attack, subsequent histologic examination shows the condition known as otitis interna ossificans with atrophy of the 8th nerve and of the nerve endings[37]. Microscopic examination of the brain has in some cases shown degeneration of the nuclei and nerve fibers along the intracranial course of the 8th nerve. Apart from hemorrhage into the labyrinth, deafness in cases of leukemia may also occur because of leukemic infiltration of the cochlea and cochlear nerve. This is observed commonly in cases of myeloid leukemia. Druss[24] believes that the aural complications of leukemia are more prevalent than is generally believed. They occurred in 25 of 148 cases reviewed, or in 16.8%. The 2 chief lesions of the external ear were ulceration of and hemorrhage from the membrane and the bony canal wall. The tympanomastoid regions were involved in 12 instances, the predominant lesions here being hemorrhage and inflammatory reaction. The inflammatory reaction may produce extensive suppuration within the mastoid bone. The internal ear was the site of involvement in 9 cases, and this was manifested by hearing impairment of the nerve type, nystagmus, vertigo and partial or total loss of vestibular function. In 3 cases both the middle and inner ear were involved. Facial paralysis was observed in 1 case. Druss noted that pathologic changes in the ear in leukemia may be found on histologic examination even in cases without any clinical evidence of aural disease. Interestingly enough, otitic infections are more severe in the leukemic than in the nonleukemic patient and they not infrequently show a tendency toward early invasion of the adjacent structures. These severe and fulminating infections in patients with leukemia can best be attributed to an impairment of the immunity of the tissues in leukemia.

LYMPHADENOPATHY. Enlarged lymph

nodes in the region above the clavicle will come to the attention of the otolaryngologist either because of a specific complaint of swelling or mass, or they will be discovered during the course of examination for some condition of which lymphadenopathy is a feature. It must be recognized that in infants and children a great prominence of the lymphoid structures is normal and allowance must be made for this in the evaluation of lymphadenopathy in the young. On the other hand lymphadenopathy in the adult is practically always due to some disease.

Cervical lymphadenopathy of short duration usually indicates an acute process due to some inflammatory condition in the regions drained by the nodes. Enlargement of longer duration is associated with chronic inflammation or primary disorder of the lymphatic tissues. Infections of the ear, nose, mouth and throat usually cause a chain of small, discrete, at first soft, later hard nodes in the anterior or posterior region, either unilateral or bilateral. The submaxillary, sublingual and postauricular lymph nodes are also variously involved. Kennedy[57] has emphasized that in children the cervical nodes are the seat of more than 90% of acute inflammatory disease of the lymphoid tissues. These nodes are enlarged in tonsillitis, scarlet fever, and other infectious fevers, stomatitis, dental eruptions, and infectious and superficial infections of the scalp and infections of the ear. In retro-pharyngeal abscess in the young child, not infrequently a lymph node in the upper posterior triangle of the neck assumes a considerable size and becomes tender. On the other hand in chronic cervical adenitis in children due to chronically infected tonsils or adenoids, or both, the lymph nodes which may be considerably enlarged are not appreciably tender.

Infectious mononucleosis is a disease entity frequently first observed by the otolaryngologist. It is characterized clinically by fever, lymphadenopathy and the symptoms of acute respiratory infection. Enlarged and often tender nodes of the neck are the ones most frequently involved. The postcervical nodes are enlarged in 88% of the cases, subangular in 64%, submaxillary 52% and submental 10%. The nodes are firm and discrete and never fluctuant. In some cases the involved nodes may be beyond the palpating fingers. Fever is present at some time in the course of the disease in approximately 100% of the cases. Symptoms referable to the nose and throat are observed in practically every case. They vary in intensity from a mild rhinitis or pharyngitis to ulcerative, follicular, or membranous tonsillitis or Vincent's angina. According to Sturgis[120], about three-fourths of the patients have some objective evidence of such an infection, including injection of the pharynx, hyperplasia of the lymphoid tissue and occasionally membrane formation. The laryngologic aspects of infectious mononucleosis have been stressed by Grove[42]. Because of the localized swelling a diagnosis of peritonsillar abscess has been made. This swelling is due to the fact that all the lymphoid structures of Waldeyer's ring become hypertrophied to a marked degree and in these cases the mistaken diagnoses may have been due to hypertrophy of the lymphoid tissue of the pharyngeal bands. In many cases a membrane develops which may be restricted to individual locations but may also involve the entire pharynx. The process may not stop with injection of the mucous membrane, hypertrophy of the lymphoid tissue and membrane formation. It may at times go on to actual ulceration. The occurrence of edema of the larynx and pharynx as a complication of infectious mononucleosis is associated with hoarseness and marked

dyspnea[109]. The respiratory symptoms include sore mouth, sore throat, cough and thoracic pain. The characteristic lymph node shows hyperplasia of the lymphoid reticulum and germinal centers, often to the point of distorting the nodal architecture. Many of the lymphocytes are atypical. Some enter the peripheral blood, but they need not be present early in the disease. The disease involves the lymphoid tissue of all the organs and tissues of the body with the exception of the bone marrow[20]. The reticulum of the bone marrow usually does not undergo lymphoid hyperplasia. The marrow may be normal or show a myeloid hyperplasia[69]. The diagnosis of infectious mononucleosis depends on the demonstration of the heterophil antibody titration[22] and the finding of atypical lymphocytes in the blood. A smouldering form of the disease may exist for months, and atypical lymphocytes have been noted in the peripheral blood for as long as several months to several years after clinical recovery. On the other hand lymphadenopathy may persist for months after the atypical lymphocytes have disappeared from the blood. The disease may be very mild or very severe. Infectious mononucleosis may simulate many other diseases such as acute tonsillitis and other acute pharyngitides, tuberculous adenitis, syphilis, agranulocytosis, the lymphoblastomas, acute leukemia, infectious hepatitis, meningitis, acute appendicitis and brucellosis. False positive serologic reactions for syphilis appear in 18 to 20% of all patients with infectious mononucleosis. The positive reaction persists only a few days to a few weeks but occasionally it may be present as long as several months.

In most instances a generalized progressive enlargement of the lymphoid tissue speaks for a lymphoblastoma. The child or adolescent patient with Hodgkin's disease may be seen first by the otolaryngologist or dentist in the belief that the cervical adenopathy is secondary to dental infection, gingival hypertrophy, gingival bleeding and secondary infection with the fusospirochetal organisms which are not uncommon in patients with the condition. Hodgkin's disease is a chronic disease which is characterized by painless and progressive enlargement of the lymph nodes and the organs of the reticuloendothelial system, fever, anemia and general wasting. The onset of the disease is gradual. An acute upper respiratory infection, an acute exanthematous fever or alveolodental abscess may procede the increasing weakness, pallor and fever which is constant and remittant in nature. Itching of the skin is an important symptom and may precede the lymphadenopathy. The presenting symptom in about 79% of the cases is painless progressive enlargement of a lymph node or nodes involving most frequently the cervical nodes on one side. The supraclavicular, axillary and inguinal nodes are also especially involved. Enlargement of the superficial nodes is evident to the eye. Enlargement of the lymph nodes and their pressure phenomena are early and prominent symptoms in 60 to 75% of the cases[26]. Enlarged nodes in the mediastinum may cause cough and dyspnea. Hoarseness is a common finding due to pressure on the recurrent laryngeal nerves and many patients also complain of difficulty in swallowing. The lymph nodes in Hodgkin's disease and lymphosarcoma are soft to firm in consistency depending upon the stage of the disease. They remain discrete and practically never show any tendency to break down. While Hodgkin's disease at its onset tends to involve only a single group, or 2 or 3 groups of nodes, lymphosarcoma and leukemia in general tend to affect numerous groups of

nodes. The differential diagnostic problem[25,112] involves giant follicular lymphoblastoma, myeloid and lymphatic leukemia, lymphosarcoma and reticulum cell sarcoma, metastatic carcinoma, Boeck's sarcoid, non-specific inflammatory adenopathy, certain fungus diseases, typhoid, brucellosis, tuberculosis, syphilis and infectious mononucleosis. There are no characteristic hematologic findings in Hodgkin's disease[68]. In some cases of lymphosarcoma the peripheral blood may show a leukemic blood pattern (lymphosarcoma cell leukemia). The final diagnosis rests with the histopathologic appearance of diseased tissue. In a typical case the microscopic examination of the lymph node of Hodgkin's disease will show reticuloendothelial hyperplasia, giant cells, eosinophils, necrosis and fibrosis, the proportion of these varying with the stage of disease. Both Hodgkin's disease and lymphosarcoma are so highly radiosensitive that the response is sufficient to distinguish them from other types of adenopathy. In practically all cases of leukemia rather slow and painless general enlargement of lymph nodes also occurs. Fever, prostration, pallor, enlargement of the spleen, liver, hemorrhagic manifestations, gingivitis and ulcerations of the oral cavity that occur in leukemia should give strong hint as to the cause of the lymph nodes. Studies of the blood and bone marrow will in most cases establish the diagnosis. At times enlarged lymph nodes of the neck may be the only evident sign of carcinoma in adjacent organs. In several cases with chronic, painless enlargement of the cervical lymph nodes, biopsy revealed the presence of metastatic carcinomatous involvement, the primary source of which was found in the thyroid gland.

Hemorrhagic Diseases. Hemorrhage into or from the mucous membranes of the nose, gums, throat and ears may be the first sign of a disorder of the hemopoietic organs. In some hemorrhagic conditions the bleeding is the symptom of a recognized local disease, in others it is the manifestation of a systemic disorder. In general, the mechanism of abnormal bleeding results from one or more of the following factors: 1, quantitative and qualitative changes in the blood platelets; 2, disturbances in the clotting mechanism, and 3, increased permeability of the capillary wall. The organs and cells involved in the hemorrhagic disorders are the bone marrow megakaryocytes which produce the blood platelets which in turn furnish thromboplastin; the liver which furnishes prothrombin, fibrinogen and heparin; and the blood vessels with their contractile function and capillary reactions.

Hereditary hemorrhagic telangiectasis may be limited to the face, lips and mucous membranes of the oral cavity[30,117], or may involve the gastrointestinal, respiratory or genito-urinary tracts. Epistaxis is common and bleeding may arise spontaneously or following slight trauma or vasomotor disturbance[138]. The telangiectases may be pinpoint in size or large. "Spider" angioma tumors are observed particulary in elderly patients. The bright-red violaceous or purple telangiectases are seen on the face, lips, tongue, conjunctivae, ears, finger-tips and feet. Small telangiectases may resemble purpuric spots. The vascular lesions are generally brighter in color and somewhat raised above the surface. They fade on pressure and unlike purpuric lesions are permanent. The walls of the vessels are extremely thin, consisting practically of merely a layer of endothelium. Dilation of the capillaries and venules with no deficiency of elastic tissue has been described[138]. The telangiectases have been found in the pharynx, larynx, trachea, stomach and duo-

denum at autopsy. Except for the hypochromic anemia due to chronic hemorrhage the blood is not characteristic. An atavistic type of hereditary hemorrhage telangiectasis has been described by Peluse[102] in a 67 year old white male with gingival bleeding and oral manifestations of the disorder. Hemangiomas[31,134] are often encountered about the face and neck, and those presenting externally may also involve the oral cavity. Their occurrence in the nasal cavity and paranasal sinuses are uncommon but when present constitute a diagnostic problem because they are subject to trauma, acute inflammatory processes and even fatal hemorrhage.

Massive hemorrhage as an otolaryngological complication was reviewed by Motley[88] who reported 7 cases with 6 fatalities. Fatal hemorrhage may follow complications of deep neck infections; bleeding from the throat may be associated with peritonsillar or pharyngomaxillary infection; and bleeding from the ear, associated with throat or neck infection and swelling, has been reported. Immediate ligation of the carotid artery may be life saving in some of these conditions. Massive epistaxis requiring ligation of the external carotid artery has been reported[48].

Spar and Hallberg[115], reviewing 106 cases of severe epistaxis treated at the Mayo Clinic, stated that, with 50% of the patients 55 years of age or more, 40% had hypertension or arteriosclerosis or both. In one-half of the cases the bleeding was from the anterior portion of the septum. Analysis of the 106 cases revealed the causes of the epistaxis in the following order of frequency: undetermined, hypertension, arteriosclerosis, hypertension and arteriosclerosis, trauma, familial hemorrhagic telangiectasis, post-infection, general debility, post-operation, blood dyscrasia, and malignant lesions. The cause of the epistaxis could not be determined in 27% of the cases. A case of idiopathic epistaxis was reported by Salinger[111].

Nievert[92a] and others believe that many cases of so-called idiopathic epistaxis are on the basis of prothrombin or ascorbic acid (subclinical scurvy) deficiencies or that these deficiencies are at least contributing factors.

Bleeding following tonsillectomy and the effects of acetylsalicylic acid chewing gum and vitamin K on secondary tonsillar bleeding have been the subject of a number of reports[92a,93,114]. Nievert's[94,95] observations suggest that the most common cause of late secondary tonsillar hemorrhage is a reduction in the prothrombin of the blood brought about by the use of acetylsalicylic acid or salicylates. However, with the simultaneous administration of vitamin K the prothrombin lowering effect of acetylsalicylic acid is overcome and consequently normal coagulation takes place. Evidence has been presented that the administration of vitamin C also prevents salicylate-induced hypoprothrombinemia through the detoxifying action of ascorbic acid. On the other hand Livingston and Neary[76] found that the routine post-tonsillectomy use of chewing gum containing acetylsalicylic acid does not give rise to prothrombinopenic hemorrhage or have any adverse effect on blood prothrombin. Fox and West[34] reviewed a series of 687 cases of tonsillectomy and adenoidectomy and listed the causes of secondary hemorrhage as follows: acute febrile diseases occurring during convalescence; dietary deficiencies, particularly of vitamins and proteins; hypertension; local infection; local trauma; blood dyscrasias, and certain drugs.

Pallor and rapid pulse associated with a marked neutrophilic leukocytosis (as high as 50,000 per c.mm.) and hemoconcentration is significant of

early post-tonsillectomy bleeding of a critical nature.

From the standpoint of diagnosis the otolaryngologist must often consider bleeding due to thrombocytopenic purpura, aplastic anemia, acute leukemia and hemophilia[66]. Purpura is a symptom manifested by hemorrhages into the skin, subcutaneous tissues, body cavities, joints and from the mucous membranes and from points of trauma. It has been emphasized that thrombocytopenic purpura is not a diagnosis, but rather a symptom complex associated with many diseases in which the history, physical examination, blood and bone marrow studies are all of great diagnostic importance. Idiopathic thrombocytopenic purpura occurs most frequently in children and young adults and in the female sex. Clinically, the onset of purpura hemorrhagica may occur suddenly but usually it is preceded by a period of easy bruising or by localized bleeding from the nose (epistaxis), gums, genito-urinary tract, profuse menstruation or menorrhagia or bleeding into the gastrointestinal tract. Intracranial hemorrhage is the most serious complication and may involve the brain or its coverings. This last is not uncommonly the cause of death and one of the most important reasons for early diagnosis. The hemorrhages are associated with a reduced platelet count, a prolonged bleeding time, and a normal coagulation time, although there is a nonretractile clot. Another finding of diagnostic importance is the presence of adequate numbers of megakaryocytes in the biopsied bone marrow[65], a finding which in most cases assures a satisfactory platelet response following splenectomy[16]. Idiopathic thrombocytopenic purpura may be simulated by various other types of purpura. Hemorrhagic states associated with a persistent leukopenia should make one suspicious of aplastic anemia, subleukemic leukemia and other blood dyscrasias. Marked splenomegaly or generalized lymphadenopathy are often associated with leukemia, lymphosarcoma, Hodgkin's disease and other secondary or symptomatic types of disease. Every effort should be made to eliminate the possibility of a food or drug idiosyncrasy as the cause of the purpura. Offending chemicals and drugs such as the sulfonamides, arsphenamine, gold salts, benzol, sedormid, dinitrophenol, quinine and organic hair dyes may cause thrombocytopenic purpura. Hemorrhagic areas in the mucous membranes of the oral cavity due to certain drugs and chemicals may be associated with inflammatory and necrotic reaction of the hemorrhagic lesions. The bone marrow pattern in secondary thrombocytopenic purpura depends upon the causative disease or agent. Conditions such as aplastic anemia, leukemia, metastatic tumor, radiation, intoxication and infections which either destroy or interfere with the development of the megakaryocytes result in thrombocytopenia and purpura. Thrombocytopenic purpura has been seen as a complication and associated with acute mastoiditis, lateral sinus thrombosis, streptococcus viridans bacteremia and multiple metastatic abscesses[136]. In hemophilia the symptoms depend upon a defect in the coagulation mechanism. It is a hereditary disease characterized by the transmission of a sex linked recessive Mendelian defect, recurring hemorrhages throughout life, occurring almost always in the male, and transmitted by females. The hemorrhages may be spontaneous or they may be initiated by some type of trauma. The most frequent sites of hemorrhage are the mouth, gums, lips and tongue. Epistaxis occurs in almost all cases. Petechial hemorrhages are

rarely seen. Subcutaneous and intramuscular hemorrhages are common. Subcutaneous bleeding may spread over as much as half the body. At the site of origin the tissue is hard, indurated, raised and purplish black. From this site the hemorrhage extends in all directions "like ripples on a pond"[10]. Hematoma of the head or neck may become very serious if they involve areas where pressure of a large mass may have grave effects. Bleeding may occur into the joints, usually followed by varying degrees of bone destruction and deformity. Except for the prolonged coagulation time, all the blood studies are normal[70]. Anemia when present is due to the loss of blood. Bleeding states resulting from increased capillary permeability in which the platelet count is normal are observed in the anaphylactoid purpuras, chronic diseases such as nephritis, endocarditis, infections such as scarlet fever and typhoid, intoxications and avitaminoses such as scurvy.

GRANULOCYTOPENIA (agranulocytosis). An outstanding clinical feature of agranulocytosis is the necrotic lesion in the throat and oral cavity and also at times involving the mucous surfaces elsewhere. The disease is characterized by a marked reduction in the number of granulocytes in the peripheral blood. The other blood elements are not affected. It is well established that agranulocytosis in most instances is secondary to drug sensitivity. The frequent offenders are aminopyrine[60], the sulfonamide drugs, thiouracil and related compounds, gold, arsphenamine, dinitrophenol, novaldin, causalin and occasionally other drugs.

Gingivitis and stomatitis[26a] are both frequent and early symptoms of acute agranulocytosis. Histological sections of the gingival tissue in this disease have been studied only in a few cases. In a case of acute agranulocytosis[5] with aplasia of the granulopoietic elements in the bone marrow, histologic examination of the gingival papilla showed a lack of keratinization of the epithelium and edema of the deeper epithelial layers and also edema and hyperemia of the subepithelial connective tissue. The narrow zone surrounding the necrotic area was infiltrated by plasma cells, macrophages and lymphocytes. Neutrophilic leukocytes were absent. Many of the plasma cells were binucleated and trinucleated. The capillary endothelial cells were swollen and migration from the capillaries was reduced to a few lymphocytes and monocytes.

The lesions in the oral cavity usually begin with a hemorrhagic, cyanotic area which becomes sharply demarcated, necrotic and soon ulcerates. The ulcer is covered by a dirty, yellow, gray or greenish-black membrane, while the surrounding tissues may show little reaction. This appearance suggests that there is a breaking down of the tissue because of the absence of neutrophils. The areas involved are most commonly the throat, skin and digestive tract. In 30 cases of agranulocytosis Plum[104] found ulcerations of the throat in 28; the other 2 showed merely swelling and edema of the mucous membranes. The sites of necrosis in his 30 cases of agranulocytosis in order of frequency were tonsil, root of the tongue, sinus pyriformis, palatine arches, soft palate, entire pharynx, larynx, epiglottis and uvula. The bone marrow in some cases of this disease shows a myeloid hyperplasia with a failure of maturation (maturation arrest) and proliferation of the early stages of the granulocytic series. The recovery phase is marked by a rapid maturation of the immature granulocytes in the bone marrow and the finding of many toxic neutrophils in the peripheral blood. In fatal cases

of agranulocytosis there is a complete granulopoietic aplasia accompanied by a relative increase or actual proliferation of reticular cells, plasma cells, and lymphocytes. Thus sternal marrow examination offers an accurate method of evaluating the prognosis in cases of agranulocytosis[72]. Recovery is not to be expected with a complete aplasia of the bone marrow granulocytes. The onset of the symptoms is usually sudden and is marked by chill, high fever and necrotic oral lesions. There is severe prostration. Ulceration and necrosis of the pharynx are accompanied by a fetid odor of the breath. Toxemia, heart failure and death may occur in from 24 hours to one week. The prognosis of agranulocytosis has changed with the introduction of the antibiotics. Since death is due to severe toxemia associated with the lack of granulocytes, early diagnosis and institution of therapy is imperative. This disease must be differentiated from certain other ulcerative lesions of the oropharynx[43] such as acute leukemia, aplastic anemia, infectious mononucleosis, acute poisoning, acute streptococcic sore throat, Vincent's angina, follicular tonsillitis, diphtheria and syphilis. Careful inquiry concerning the use of drugs[53], a history of exposure to overdosage of Roentgen ray or radioactive substances and detailed studies of the blood and bone marrow[65] in most cases will reveal the cause of the disease. In acute leukopenic leukemia the blood and bone marrow contain immature leukocytes. The physical findings of adenopathy and splenomegaly are usually present. Aplastic anemia is associated with leukopenia, anemia and thrombocytopenia. The bone marrow is hypoplastic and shows a depletion of all marrow elements. Most infections are associated with a neutrophilic leukocytosis. Infectious mononucleosis complicated by agranulocytosis has been reported[119], but is exceedingly rare. The recent introduction of the use of folic acid antagonists in the treatment of leukemia very frequently produces ulcerative and necrotic lesions of the oral mucosa[9,73]. The lesions due to aminopterin may be associated with serious and profuse hemorrhages from the nose and gastrointestinal tract which may be uncontrollable. Deafness is a minor toxic manifestation of the drug. In patients with primary splenic neutropenia, primary and secondary splenic pancytopenia[66a] and recurrent cyclic[97] and chronic neutropenic states, a sore, ulcerated mouth and throat may develop associated with the granulocytopenia. Relief of all the symptoms following splenectomy is observed more frequently in primary and secondary splenic neutropenic and pancytopenic states[15,67]. In our patients with neutropenia, splenomegaly and rheumatoid arthritis[67] (Felty's syndrome) a history of frequent upper respiratory infections and aggravating sore throat were common complaints. In one of these cases an ulcerated lesion of the oral mucosa developed into a noma-like lesion.

Miscellaneous Disease. The highly colored mucous membranes of the oral cavity and especially the peculiar color of cyanosis of the face, lips, hands and feet are characteristic of polycythemia vera[71]. The conclusive diagnosis is furnished by the physical findings and laboratory studies. Purpura of the skin and membranes in this disease may arise either spontaneously or following slight trauma.

Lesions of disseminated lupus erythematosus occur on the oral mucosa in about 15% of the cases. The oral manifestations which usually develop after the skin lesions have made their appearance are observed on the lips, tongue, oral mucosa of the cheek and the soft palate. The gums are rarely

involved. The finding of the "LE" cell in the bone marrow in suspected cases of acute disseminated lupus erythematosus is of diagnostic aid in cases in which the classic dermatologic manifestations are lacking[7,46,47].

Histoplasmosis of the oropharynx and larynx may occur as a primary local lesion[38,123] or as part of a systemic involvement. When the lesions appear in the larynx the differential diagnosis must be made between histoplasmosis and carcinoma, tuberculosis, syphilis and the various fungus diseases. In a review of 73 cases of histoplasmosis Parsons and Zarafonetis[98] reported 10 instances of granulomatous and ulcerative lesions occurring in the larynx, usually in association with lesions of the pharynx. Hoarseness is a common symptom when the larynx is involved. The diagnosis is made by histologic sections or cultures from laryngeal lesions.

The various types of xanthomatoses may result in lesions involving the ear, mouth, throat, larynx and trachea[40,63,85,110]. These granulomatous masses of lipoid cells may produce pressure symptoms and destructive lesions of the skull. Schuknecht and Perlman[113] emphasize the significant fact that uncomplicated lesions of Hand-Schuller-Christian disease or eosinophilic granuloma of the temporal bone are almost always painless. Furthermore, when secondary infection occurs in such a diseased temporal bone, the primary disease process is often overlooked. Biopsy establishes the diagnosis.

Conclusions. Diseases of the hemopoietic organs are often manifested by local signs and symptoms. The correlation of the clinical findings and hematological studies are essentially for an accurate diagnosis, prognosis and treatment. An understanding of the physiologic-pathologic mechanism involved in disorders of the blood is of importance to the otolaryngologist as he may be the first to observe the local or early changes of the systemic process[62,74].

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PROCEEDINGS OF

The Physiological Society of Philadelphia

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The Lactic Acid Oxidising System of Escherichia coli. NIELS HAUGAARD, Ph.D. (John Herr Musser Dept. of Research Med., Univ. of Penna.). The mechanism of lactic acid oxidation by E. coli (Strain B) was studied. The organisms were grown in media containing D,L-lactate as the source of carbon. Cell free preparations were obtained by exposing suspensions to sonic vibration. Such preparations under aerobic conditions were found to convert D,L-lactic acid quantitatively into pyruvic acid. In experiments in which the reaction was allowed to go to completion, an exact balance was obtained between the lactic acid added, the oxygen taken up, and the pyruvate formed.

The entire metabolic activity was associated with particulate matter, the supernatant, after high speed centrifugation, having no activity. A complete hydrogen transferring system was apparently situated on the suspended particles since the preparations oxidized lactate in the absence of added hydrogen carrier. Addition of methylene blue did not further increase the activity.

An acetone powder was prepared from the suspensions obtained by sonic vibration. A suspension of such an acetone powder was inactive in the absence of added methylene blue. When methylene blue was added, it converted half of added D,L-lactate to pyruvate. It was inactive in the presence of L-lactate.

It is concluded that both D- and L-lactic dehydrogenases are present in E. coli. Precipitation with acetone destroys the system, oxidizing L-lactic acid as well as part of the hydrogen transferring enzymes.

The experiments demonstrate the usefulness of sonic disintegration in the study of enzymes.

It is suggested that by utilizing enzyme preparations such as those described here, analytical methods might be developed for the quantitative determination of D- and L-lactic acids.

A Method of Administering Carbon Dioxide at a Constant Degree of Induced Anoxemia. RAYMOND PENNEYS, M.D. (Depts. of Prev. Med. and Med., Johns Hopkins School of Med.). A method is described whereby a fixed concentration of carbon dioxide can be administered with a constant degree of induced anoxemia. It is a modification of a procedure previously described (Bull. Johns Hopkins Hosp., **84**, 430, 1949) in which a low oxygen gas of variable oxygen concentration, with oximeter control, was used to induce and maintain a constant degree of anoxemia. The modification consists of placing 2 additional tanks in circuit, one with nitrogen and another with oxygen, each containing the desired concentration of carbon dioxide. By changing from the pure nitrogen and pure oxygen tanks to those containing the CO_2 gases, subjects were studied at various levels of anoxemia with or without CO_2 in the inspired gas.

Twenty-six tests were done on normal subjects with 5% CO_2 mixtures.

In all instances the arterial oxygen saturation was just as stable as that obtained with the plain O_2-N_2 gases, despite the marked hyperventilation brought on by the 5% CO_2. The systolic and diastolic blood pressure increases at levels of 85, 80, 75 and 70% arterial saturation were greater with the CO_2 gases than with the O_2-N_2 gases. Also the T wave (Lead II) was lowered to a greater extent with CO_2. Symptoms of fainting or dizziness, when encountered with the plain O_2-N_2 gases, always disappeared on the addition of 5% CO_2.

In 8 tests, 2.5% CO_2, instead of 5% CO_2, has been used and has been found to be sufficient to relieve such symptoms. The CO_2 concentration of the expired gas, obtained while the subject is breathing the O_2-N_2 gases, has been analyzed in a few tests.

The Blood Flow and O_2 Consumption of the Human Brain in Hyperthyroidism. L. Sokoloff, M.D., R. L. Wechsler, M.D., K. Balls, M.D., R. Mangold, M.D., and S. S. Kety, M.D. (Dept. of Physiol. and Pharmacol., Univ. of Penna. Grad. Sch. Medicine, and Endocrine Clinic, Univ. Hospital). Hyperthyroidism is accompanied by an increase in total body O_2 consumption which is generally attributed to an augmented metabolism in all organs and tissues. In order to determine the extent of participation of the brain in this elevated metabolic rate, the cerebral blood flow and O_2 consumption of 9 hyperthyroid patients were determined by the nitrous oxide method. The diagnosis was made on the basis of the clinical picture, B. M. R., protein bound iodine in the serum, and the uptake of radioactive iodine by the thyroid gland. A B. M. R. determination was made following each cerebral blood flow study.

The B. M. R. in this group of patients varied from +30% to +88%. The results of the cerebral studies were compared to those obtained by Kety and Schmidt on 14 normal subjects. The mean arterial blood pressure of 107 mm. Hg exceeded the normal mean of 86 by a significant amount ($p<0.01$). This is probably the explanation for the increase in the mean cerebral blood flow of 65 cc./100 gm./min. which exceeded the normal mean of 54 by an amount approaching significance (p between 0.1 and 0.05) since the mean for cerebral vascular resistance of 1.8 mm. Hg./cc./100 gm./min. did not differ significantly from the normal mean of 1.6. The most interesting result, however, was the close approximation between the mean value for the cerebral O_2 consumption of 3.4 cc./100 gm./min. and the normal mean of 3.3. In addition, a complete lack of correlation between total body O_2 consumption, as manifested by the B. M. R., and the cerebral O_2 consumption was found ($r = -0.027$).

The obvious conclusion is that the brain does not share in the augmented O_2 consumption of the body in hyperthyroidism.

Biosynthesis of Radioactive Fatty Acids and Cholesterol. Roscoe O. Brady, M.D., and Samuel Gurin, Ph.D. (Dept. of Physiolog. Chem., School of Medicine, Univ. of Penna.). We have studied the biological synthesis of long chain fatty acids and cholesterol by incubating slices of liver tissue from fed rats of the Wistar strain in the presence of C^{14}— labeled acetate, pyruvate, butyrate, hexanoate, and octanoate as substrates. The usual procedures for the isolation of fatty acids and cholesterol were followed. Fatty acids whose chain lengths were longer than 10 carbon atoms were separated by precipitation with a copper-lime mixture and effectively freed from contaminating substrate. All of

the substrates investigated contributed carbon atoms for long chain fatty acid and cholesterol synthesis *in vitro*. The addition of amorphous insulin to the incubating medium increased significantly the amount of acetate incorporated into long chain fatty acids. It would appear that all of the short chain fatty acids we investigated are as efficiently converted to long chain fatty acids as is acetic acid. The long chain fatty acids derived from carboxyl labeled octanoate appear to contain C^{14} in alternating carbon atoms throughout the molecule. These results suggest that the synthesis of long chain fatty acids from short chain acids probably occurs by fragmentation of these acids to 2-carbon units which are subsequently recombined to form long chain fatty acids.

BOOK REVIEWS AND NOTICES

THE VITAMINS IN MEDICAL PRACTICE. By J. SHAFAR, M.D. Pp. 383. London and New York: Staples Press, 1949. Price, $4.50.

THE special value of this book is in its assemblage of all the significant work in the field of vitamins and vitamin therapy. It is concise and practical and its preparation has obviously entailed much work.

The contents are divided into 3 parts. The first deals with each vitamin separately as to natural origin, effect of heating, and its toxic and pharmacological action. The second division deals with specific and established vitamin deficiency syndromes. Following this the bulk of the book is devoted to the practical issues of vitamin therapy in clinical practice. The clinical condition is the primary consideration, and the vitamins are discussed in relation to it, though one finds throughout the results of various animal experiments.

The style is good and the information correct. There is an extensive bibliography. The book can be recommended as a reference book as well as being profitable for reading.

H. V.

LIVING WISELY AND WELL. By WILLIAM B. TERHUNE, M.D., DOUGLAS A. THOM, M.D., KENNETH E. APPEL, M.D., and WINFRED OVERHOLSER, M.D., Sc.D. Pp. 95. New York: E. P. Dutton, 1949. Price, $2.00.

THE 4 chapters in this wise little book were "presented to the public" by the Silver Hill Foundation of New Canaan, Connecticut, in a series of lectures on mental hygiene. It seemed appropriate, therefore, to get the opinions of some non-medical readers before preparation of this review. They all agreed that the simple treatment was easily comprehended and held their interest—mental hygiene is prominent in people's minds these days—and that they felt that they had profited from reading it. That made it unanimous, as to me also it seems one of the most useful presentations of the subject that has come my way. One may prefer Dr. Thom's application of the principles of mental hygiene to the problems of childhood; another, Appel's discussion of mental hygiene for the adult in the world of today; still another, Overholser on the same for later maturity—a euphemism that soon becomes replaced by "old age" in the text; to me, the rather lengthy Editor's Preface provided the most provocative yet satisfying reading of the lot—no reader of the book should omit it.

All the authors are well known psychiatrists and authorities in their field. One might well have hoped that they would produce this sane and optimistic philosophy of life (together with techniques for avoiding distressing emotional disturbances), as well as conquering those already established. It is good that such hopes have not been disappointed.

E. K.

THE DIAGNOSIS AND TREATMENT OF ADRENAL INSUFFICIENCY. By GEORGE W. THORN, M.D., Hersey Prof., Harvard Medical School. Pp. 180; 32 ills., 2 in color. Springfield, Ill.: Charles C Thomas, 1949. Price, $5.50.

THIS is a concise and lucid summary of the clinical diagnosis and treatment of adrenal insufficiency, including an introductory survey of the physiology and chemistry of the adrenal. Special aspects are illustrated by cases from the Author's extensive clinical experience. Tests useful in diagnosis are explained in detail. An interesting minor point is an itemized statement of the financial burden carried by a patient with Addison's disease.

Though small in size, the book contains a great deal of practical and detailed information of interest to the practicing physician and to those concerned with theoretical aspects of adrenal cortical dysfunction.

I. Z.

DIFFERENTIAL DIAGNOSIS OF CHEST DISEASES. By JACOB JESSE SINGER, M.D., Pp. 344; 171 ills. Phila.: Lea & Febiger, 1949. Price, $7.50.

THIS is a well prepared monograph on diseases of the chest, supported by an adequate bibliography. The section devoted to the tracheobronchial tree and lungs occupies two-thirds of the text, and covers both acute and chronic pulmonary disease. Cardio-vascular diseases of the chest are not included. The book is for the general practitioner rather than the specialist, and its text is clear and concise. It is read easily and should help the physician in early diagnosis. The text includes a brief consideration of a number of pulmonary diseases rarely encountered in general practice, but fails to include a number now being

recognized with increasing frequency. An adequate discussion of the so-called collagen diseases of the lung would have improved the scope and usefulness of the text. S. S.

OPHTHALMIC MEDICINE. By JAMES HAMILTON DOGGART, M.D., Hosp. for Sick Children, London. Pp. 329; 87 ills., 28 color plates. Phila.: Blakiston, 1949. Price, $8.00.

THE title "Ophthalmic Medicine" is unsuitable for this book which deals with those phases of ophthalmology in which the eye is only part of the general disease. "Medical Ophthalmology" would have been a better title, and indeed the book is intended as a sequel to the well known "Medical Ophthalmology" of R. Foster Moore, which is now out of print.

Doggart's well written book contains a great deal of information for the general practitioner. It attempts to cover neuro-ophthalmology as well as medical ophthalmology and in so doing spreads some of the material rather thin. It is to be hoped that in future editions the Author will enlarge the sections on medical ophthalmology. The small chapter on allergy might likewise be omitted. F. A.

MEMORIES OF EIGHTY YEARS. By JAMES B. HERRICK, M.D. Pp. 270; 28 ills. Chicago: University of Chicago Press, 1949. Price, $5.00.

THESE pleasant memories are written in such an informal style, that they remind one of a genial after dinner chat about old times. Dr. Herrick introduces innumerable anecdotes and personal adventures to form a background for comments upon the conditions of medicine and surgery, as he saw them in Chicago during the latter part of the 19th and early 20th centuries. As a student, a general practitioner, a successful teacher and a distinguished consultant, he has had ample opportunity to become intimately acquainted with the situation and out of the fulness of his experience he offers much practical advice to young physicians. In the course of his long life Dr. Herrick has naturally been in close contact with many eminent surgeons and physicians, and the characterization of these many men whom he portrays in thumb nail sketches is remarkable for its astuteness and penetrating comprehension.

With his innate modesty, however, Dr. Herrick gives scant attention to his own outstanding accomplishments. He does mention his innovations in teaching, and refers to his description of sickle cell anemia, probably the first recorded, but there is little more than a brief account of his famous report on coronary thrombosis, which was received at first with such disheartening neglect, but which later received such wide recognition.

In the final chapter, Dr. Herrick's gentle reflections on old age, with his references to Ecclesiastes, a book which he has read fondly since boyhood, make a charming conclusion to this pleasant volume of recollections. At the age of 87 he discovers in his tolerance, hopefulness and from the exuberance of his youthful spirit that: "things are not so bad, after all; they might be worse. Why not, like the sundial in the garden, count only the sunny hours? Hearing is dull but I can still hear the voices of the birds and the laughter of children. Eyesight enables me to see the mountains and flowers in the garden of my Vermont summer home and to read a clearly printed page". Let us hope that these pleasures be granted Dr. Herrick unimpaired for many years to come.
W. L.

DISEASES OF THE HEART. By CHARLES K. FRIEDBERG, M.D., Lecturer in Medicine, Columbia Univ. Pp. 1081; 79 figs. Phila.: W. B. Saunders, 1949. Price, $11.50.

THIS is the most comprehensive single-volume text on diseases of the heart in the English language. The 6 parts deal with the following topics: 1, circulatory failure and the compensatory mechanisms that tend to prevent it; 2, the cardiac arrythmias; 3, the coronary circulation and disturbances in the cardiac blood supply; 4, structural abnormalities of the heart; 5, the etiologic forms of heart disease; 6, the relation of pregnancy, surgery, and insurance and medico-legal problems to cardiac patients.

The most serious omission is the lack of a discussion of the variation of the different aspects, save the roentgenologic, of the normal heart. This makes it impossible for the reader to appreciate the significance of quantitative changes. Because of this lack, the electrocardiographic discussion in Chapter 3 is hardly intelligible to the beginner and inadequate for the advanced student. Similarly, the electrocardiographic patterns of infarction and the significance of abnormal heart sounds cannot be evaluated without a knowledge of the variability of the normal. The Author fails to emphasize that every manifestation of circulatory failure may also be present in the non-cardiac and that some of these manifestations, like edema, occur

more commonly in the non-cardiac. It does not seem justifiable to introduce diagnostic methods, such as electrokymography, without discussing the validity and the reliability of the method.

In the next edition, the Reviewer would like to see greater emphasis on psychosomatic aspects in individuals with heart disease, more illustrations, and a summary and diagnostic profile for each disease, to help crystallize the clinical picture for the beginner.

These criticisms do not detract from the great value of this book. It is clearly written and remarkably free of errors. The Author avoids the pitfalls of a unilateral approach to circulatory failure, and his summary is scholarly, appealing and in harmony with present knowledge. His descriptions of pathologic anatomy are thorough and accurate. All factual statements are documented by references at the end of each chapter. The references are exhaustive of the important cardiac literature and are by themselves worth the price of the book. It is recommended to everyone interested in cardiology. L. S.

THE BIOLOGY OF MENTAL DEFECT. By LIONEL S. PENROSE, M.D. Preface by J. B. S. HALDANE, F.R.S. Pp. 285; 7 ills. New York: Grune & Stratton, 1949. Price, $4.75.

FOR anyone interested in or concerned with problems connected with the feeble minded—whether from the point of view of the individual patient, the family, the school, the institution or the entire community—this book contains a wealth of important information. It will be of value, therefore, to physicians, social workers, sociologists, and perhaps even to those who frame our laws in regard to the care of patients with mental defects. The book contains a wealth of material on the historical background of the problem, the principles of classification and causation, the important considerations—genetic and otherwise—of the various types of defects, and the theoretical as well as practical aspects of coping with the problem in terms of our present culture. A useful and fairly extensive bibliography is included. W. P.

MEDICAL CLINICS OF NORTH AMERICA. Philadelphia Number: *Medical Emergencies and Nutritional Disorders.* November, 1949. Pp. 1499-1806. Index 1947-1949. Phila.: W. B. Saunders. Price, $15.00 a year.

THE present number contains 2 Symposia, one from the Pennsylvania Hospital on Acute Medical Emergencies; and the 2d from the Philadelphia General Hospital on Nutritional Disorders. The topics under the various headings are expertly discussed, with special reference to diagnosis and treatment. The volume will be of assistance to the practicing clinician. P. G.

HUANG TI NEI CHING SU WEN, THE YELLOW EMPEROR'S CLASSIC OF INTERNAL MEDICINE. Chapters 1-34 Translated from the Chinese with an Introductory Study, By ILZA VEITH, M.A., Ph.D., Lect. in the Hist. of Med., Univ. of Chicago. Pp. 253; 24 ills. Balt.: Williams & Wilkins, 1949. Price, $5.00.

THE tardy advance of modern scientific medicine in most eastern countries is seldom disputed, at least in the West. As a result the medical care of the most populous countries of the world lags, at least to western eyes, a belief that is supported by available statistics. The medical systems of the past, as Sigerist points out in the Foreword of this entertaining book, still control medical practice, so that a good understanding of them is of great importance, not merely to the medical historian, but to the modern physician and to all those concerned with the world's health and the civilizations rooted in the distant past.

Especially does this apply to China with its close adherence to tradition, here further complicated by the special difficulties of the Chinese written language. This "Classic of Internal Medicine", then, has far more than historical interest, regardless of its uncertain date of origin and authorship.

Sigerist speaks of it as the most important of early Chinese medical works, whose medical theories still remain dominant in Chinese indigenous medicine, and compares it to the classics of Ayurvedic medicine and the Hippocratic Corpus. In English translations it has thus far been represented only by short passages. Dr. Veith's translation of the 1 to 34 chapters of the *Su Wên* fills two-thirds of the book. Her first 100 pages of comment on the philosophic, anatomic, physiologic, and therapeutic concepts contained therein and on the diseases and diagnoses covered will be of chief interest and value to most readers. In view of the difficulties and variations involved, it is surprising and especially unfortunate that a complete lack of index greatly hampers the use of the book and comparisons with other works on Chinese medicine. Wong and Wu, for instance, include in the *Nei Ching* the *Ling Shu* (Mystical Gate) as well as the *Su Wên* (Plain Questions) and name 81 chapters of the

latter, which can only be partially correlated with the Veith arrangement of 34 chapters, and that with great difficulty.

The book is beautifully prepared and "s.b.o.t.s.o.a.t.i.i.t.s." (*i.e.*, "should be on the shelves of all those interested in the subject"). We are very glad to have our copy there.

E. K.

CLINICAL INTERPRETATION OF LABORATORY TESTS. By RAYMOND H. GOODALE, M.D., Pathologist, Worcester, Mass. Pp. 622; 107 ills. Phila.: F. A. Davis, 1949. Price, $6.50.

As the title implies, this book is mainly concerned with the interpretation rather than the methodology of laboratory data. Of its 2 sections, the first presents normal and pathological values of body fluids and excreta and describes the procedures of several functional tests. Of value are many tables enumerating the various diseases which manifest similar findings such as hyperglobinemia and eosinophilia. The second half is arranged according to organic systems. The underlying pathophysiology of each disease is briefly mentioned and the characteristic laboratory findings enumerated.

G. R.

A TWENTIETH CENTURY PHYSICIAN. Being the Reminiscences of SIR ARTHUR HURST, D.M., F.R.C.P. Foreword by Prof. JOHN A. RYLE, M.D., F.R.C.P. Pp. 200; 16 ills. Balt.: Williams & Wilkins, 1949. Price, $3.50.

THESE pleasant reminiscences were never completed, for Sir Arthur Hurst died suddenly in 1944 leaving the manuscript unfinished. The task of editing and publishing was entrusted to Professor Ryle, who has prepared an appreciative foreword to the volume. The major portion of the biography deals with the education and earlier activities of Hurst; while the latter part of his interesting life is unfortunately recorded only in fragments. Even so, the memoirs furnish an intimate record of the work and relaxations of this versatile and intelligent physician and are written with such delightful humor and wit that they afford very pleasant reading.

W. L.

MICROBIOLOGY. By FLORENE C. KELLY, M.S., Ph.D., Assoc. Prof. of Bacteriology, Univ. of Oklahoma, and K. EILEEN HITE, Ph.D., M.D., Formerly Ass't Prof. of Bacteriology, Univ. of Chicago. Introduction by G. M. DACK, Ph.D., M.D. Pp. 607; 185 ills. New York: Appleton-Century-Crofts, 1949. Price, $6.50.

THE book begins with a section on the nature of microorganisms (protozoa, algae, fungi, bacteria, rickettsiae, and viruses), followed by a second part which is devoted to the methods of studying microorganisms, with a section in the appendix listing formulae for culture media, stains, and reagents. The physiology of bacteria, the development of bacterial populations, and antimicrobial agents are each dealt with in separate sections. Over half of the book is devoted to the relation of microorganisms to disease, the pathogenic microorganisms, epidemiology and public health. The book is written for the student who needs general information on the relationship of microorganisms to man and the pathogenic microorganisms. It is not complete enough to be satisfactory for medical students or graduate students in bacteriology.

H. M.

SELECTIVE PARTIAL ABLATION OF THE FRONTAL CORTEX. By THE COLUMBIA-GREYSTONE ASSOCIATES (FRED A. METTLER, M.D., Ph.D., Editor). Pp. 517; 122 ills. New York: Paul B. Hoeber, 1949. Price, $10.00.

TOPECTOMY, the limited excision of anatomically distinct areas of the frontal cortex, improves chronic psychotics, as does frontal lobotomy, by a lessening of the pain associated with mental conflict. However, extensive psychological and psychiatric studies on 24 patients through 1 year after topectomy indicate that the undesirable side-effects of lobotomy—apathy, distractibility, loss of judgment and ambition—are minimized. Despite the relatively short follow up and small number of cases, the argument for more limited psychosurgery is impressive.

The sites for ablation were purposely varied, and it is striking that areas 9, 10, and 46, on the superior convexity of the pre-motor cortex, are implicated in all favorable results.

Because of sections covering in detail all the psychologic, laboratory and psychiatric investigations employed, along with an excellent bibliography, this volume forms a comprehensive reference work for the study of mental disease.

F. G.

INTESTINAL INTUBATION. By MEYER O. CANTOR, M.D., Grace Hosp., Detroit. Pp. 333; 138 ills. Springfield, Ill.: Charles C Thomas, 1949. Price, $7.50.

THIS book brings together a great deal of data on intestinal intubation. Very naturally it emphasizes the technique proposed by the Author. It includes, however, descriptions of other methods and presents a most interesting

chapter on "the effect of intestinal gases upon balloons of intestinal decompression tubes". It presents a very full and helpful bibliography, but unfortunately misinterprets in the text some of the available literature. Its repeated statement that Miller-Abbott (why not Miller and Abbott?) developed their tube by combining the observations of Hotz and of Jones is erroneous, since neither of them knew of those observations at the time. Although Johnston did first suggest the application of the Miller-Abbott technique in obstruction, the first report of the method was by Abbott and Johnston.

Some rearrangement of material, correction of misleading statements and avoidance of repetition would enhance the value of the book, but as it stands it should be of practical value in the further application of intestinal intubation. T. M.

NEW BOOKS

Problems of Bisexuality as Reflected in Circumcision. By HERMAN NUNBERG. Pp. 83. London: Imago Publishing Co., 1949. Price, 10s.

The Official Preparations of Pharmacy. By CHARLES OREN LEE, Ph.D., Prof. of Pharmacy, Purdue Univ. Pp. 528; 32 ills. St. Louis: C. V. Mosby, 1949. Price, $5.50.

La O(rganisación) *M*(undial) S(alud) *y la Soberania Sanitaria de las Americas.* By Prof. Dr. C. E. PAZ SOLDAN. Pp. 262. Lima, Peru: Instituto de Medicina Social de la Universidad de San Marcos, 1949. No price given.

A USEFUL account of the genesis and activities of the World Health Organization by one of the leading public health authorities and medical historians of South America. E. K.

X-ray Treatment, its Origin, Birth and Early History. By ÉMIL H. GRUBBÉ, M.D., Charter Member, Radiological Society of North America. Pp. 153; 51 ills. Saint Paul and Minneapolis: Bruce Publishing Co., 1949. Price, $3.00.

Clinical Interpretation of Laboratory Tests. By RAYMOND H. GOODALE, M.D., Pathologist, Worcester City Hospital, Mass. Pp. 622; 107 ills., 3 in color. Phila.: F. A. Davis, 1949. Price, $6.50.

Vitaminology. The Chemistry and Function of the Vitamins. By WALTER H. EDDY, Ph.D., Emeritus Prof. of Physiol. Chem., Columbia Univ. Pp. 365; 37 figs. Balt.: Williams & Wilkins, 1949. Price, $6.00.

EACH of the vitamins (including folic acid) is discussed in detail under 3 headings: biological functions, chemical nature, role in human and animal nutrition. The final chapter is devoted to a consideration of "postulated vitamins." The book will serve as a useful text for students. M. C.

Pollen-Slide Studies. By GRAFTON TYLER BROWN, M.D., Consultant on Allergy, U. S. Public Health Service. Pp. 122; 98 ills. Springfield, Ill.: Charles C Thomas, 1949. Price, $6.00.

Explorer of the Human Brain. The Life of Santiago Ramón y Cajal (1852-1934). By DOROTHY F. CANNON. With a memoir by SIR CHARLES SHERRINGTON. Pp. 303; 9 ills. New York: Henry Schuman, 1949. Price, $4.00.

Essentials of Orthopaedics. By PHILIP WILES, M.S., Secretary, British Orthopaedic Association. Pp. 486; 365 figs., 7 color plates. Phila.: Blakiston, 1949. Price, $10.00.

Allergy in Relation to Otolaryngology. Edited by FRENCH K. HANSEL, M.D. Pp. 77. Saint Paul and Minneapolis: Bruce Publishing Co., 1949. Price, $2.50.

Toxoplasmosis. By DR. C. D. BINKHORST. Pp. 163; 13 ills., 6 in color. Leiden: Stenfert Kroese, 1948. Price, $3.75.

THIS is a valuable monograph on toxoplasmosis in English. There is a complete review of the literature, together with a description of the Author's own cases, the diagnostic procedures which are useful and a summary of his observations. Ophthalmologists and pediatricians especially will find it a valuable book. F. A.

Life Among the Doctors. By PAUL DE KRUIF. Pp. 470. New York: Harcourt, Brace, 1949. Price, $4.75.

MORE flamboyant popularization of medical science and the Author's particular heroes, marred as usual by his habit of overstatement. At one point (p. 352) his own words supply the key to this habit—he appears to recognize no middle ground between over and understatement. His misstatements and misleading arguments, which one would like to think were due to ignorance of the facts, are especially unfortunate, coming from one who reaches and impresses a large number of the reading public. E. K.

Diseases of the Aorta. By NATHANIEL E. REICH, M.D., Assoc. in Med., Long Island College of Medicine. Pp. 288; 93 ills. New York: Macmillan, 1949. Price, $7.50.

IN this monograph, the aorta is discussed by an Author well qualified through his many contributions to its study. The material ranges from historical aspects, through the basic sciences, to modern diagnostic and therapeutic methods. Disputable points are rare and mainly confined to the section on congenital malformations. In general, a pleasant degree of detail without heaviness is achieved, and this book is recommended to all. H. Z.

NEW EDITIONS

Electrotherapy and Light Therapy. By RICHARD KOVACS, M.D., Prof. of Physical Medicine. 6th ed. Pp. 739; 368 ills., 1 color plate. Phila.: Lea & Febiger, 1949. Price, $10.00.

The ABC of Acid-base Chemistry. By HORACE W. DAVENPORT. 2d ed. Pp. 74; 40 figs. Chicago: University of Chicago Press, 1949. Price, $2.00.

Early Carcinoma of the Uterine Cervix. By HANSJAKOB WESPI, M.D. Translated by MARIE SCHILLER, Ph.D. 2d ed. Pp. 271; 95 ills. New York: Grune & Stratton, 1949. Price, $6.50.

The Physician's Business. By GEORGE D. WOLF, M.D., Foreword by HAROLD RYPINS, M.D. 3d ed. Pp. 563; 96 ills. Phila.: J. B. Lippincott, 1949. Price, $10.00.

Length of Life. By LOUIS I. DUBLIN, Ph.D., ALFRED J. LOTKA, D.Sc., and MORTIMER SPIEGELMAN, F.S.A., Metropolitan Life Insurance Company. 2d ed. Pp. 379; 32 figs. New York: Ronald Press, 1949. Price, $7.00.

Clinical Biochemistry. By ABRAHAM CANTAROW, M.D., Prof. of Biochemistry, Jefferson Medical College, and MAX TRUMPER, Ph.D., Commander, H(S), USNR. 4th ed. Pp. 642; 38 figs. Phila.: W. B. Saunders, 1949. Price, $8.00.

Topographical Anatomy of the Dog. By O. CHARNOCK BRADLEY, M.D. Revised by TOM GRAHAME, T.D., Lecturer on Comparative Anatomy, Univ. of Edinburgh. 5th ed. Pp. 319; 128 ills. New York: Macmillan, 1949. Price, $7.00.

The Chemistry of Organic Medicinal Products. By GLENN L. JENKINS, Prof. of Pharmaceutical Chemistry, Purdue Univ., and WALTER H. HARTUNG, Prof. of Pharmaceutical Chemistry, Univ. of North Carolina. 3d ed. Pp. 745. New York: John Wiley & Sons, 1949. Price, $7.50.

THE rapid expansion in the chemistry of medicinal and related products has resulted in a thorough revision and enlargement, by nearly 100 pages, of this standard textbook. Much new material has been included in the fields of antibiotics, antimalarials, antihistaminics, sulfonamides, and other active lines of therapeutic investigation.

H. V.

Cystoscopy and Urography. By JAS. B. MACALPINE, D.Sc., F.R.C.S. (Eng.). 3d ed. Pp. 554; 338 ills. Balt.: Williams & Wilkins, 1949. Price, $13.50.

A WELL revised edition of practical urology. The added chapter on the Pathology of Renal Tuberculosis is concise and well placed for the study of this common urologic problem. The urographic reproductions are much improved.

B. H.

Textbook of Physiology. By WILLIAM D. ZOETHOUT, Ph.D., Prof. Emeritus of Physiology, Loyola Univ., and W. W. TUTTLE, Ph.D., Prof. of Physiology, State Univ. of Iowa. 10th ed. Pp. 710; 301 ills., 6 color plates. St. Louis: C. V. Mosby, 1949. Price, $4.75.

Pain Syndromes. By BERNARD JUDOVICH, B.S., M.D., Instructor in Neurology, and WILLIAM BATES, B.S., M.D., F.A.C.S., F.I.C.S., Prof. of Surgery, Grad. School of Medicine, Univ. of Pennsylvania. 3d ed. Pp. 357; 181 ills. Phila.: F. A. Davis, 1949. Price, $6.00.

Pathology of the Nervous System. By J. HENRY BIGGART, M.D., Prof. of Pathology, Queen's Univ., Belfast. Foreword by A. MURRAY DRENNAN, M.D. 2d. ed. Pp. 364; 232 ills., 10 color plates. Balt.: Williams & Wilkins, 1949. Price, $6.00.

THIS edition follows the same general plan as the first; the text has been amply revised and new material added. An excellent feature is the Author's approach to the subject by applying the principles of general pathology to the lesions of the nervous system. Although written as a "Student's Introduction", this brief text may also be recommended to the practicing physician and those specializing in neurology.

E. G.

Practical Anatomy. By W. E. LE GROS CLARK. Prof. of Anatomy, Oxford. 2d ed. Pp. 493; 268 ills. Balt.: Williams & Wilkins, 1949. Price, $6.00.

The Arthropathies. By ALFRED A. DE LORIMIER, M.D., Radiologist, St. Francis Hospital, San Francisco. 2d ed. Pp. 335; 157 ills. Chicago: Year Book Publishers, 1949. Price, $7.00.

Directory of Biological Laboratories. By CLYDE F. BURNS. 4th ed. Pp. 140. Chicago: Burns Compiling and Research Organization, 1949. Price, $3.00.

A LISTING of laboratories of the United States concerned with biological or biochemical investigations.

Recent Advances in Physiology. By W. H. NEWTON, M.D., Prof. of Physiology, Univ. of Edinburgh. 7th ed. Pp. 269; 90 ills. Phila.: Blakiston, 1949. Price, $4.50.

THE new edition (after a gap of 20 years) of this series of books is aptly termed by the Author, "Some advances by some physiologists." There are useful sections on color vision, skin sensation, renal circulation and hypertension, pregnancy, diuresis, and physical factors of temperature control. The book should be quite valuable to senior students; it covers interesting ground and is well written.

H. B.